

REDUCTION OF VASCULAR EFFECTS AND PAIN IN AORTOFEMORAL ANGIOGRAPHY

An experimental and clinical study of second generation
of ratio 3.0 contrast media

ULF NYMAN



MALMÖ 1982

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ACKNOWLEDGEMENTS

The present investigation was designed and performed at the Departments of Diagnostic Radiology (Head: Professor T. Olin), Experimental Research (Head: Professor S-E. Bergentz) and Clinical Physiology (Head: Professor S-E. Lindell), Allmänna Sjukhuset, Malmö, University of Lund, Sweden.

I wish to express my thanks to:

Professor Erik Boijesen and Professor Tord Olin for their support
Docent Torsten Almén for invaluable guidance;
Professor Sven-Erik Lindell, Dr. Magnus Landtman, Dr. Paul Nilsson
and Mrs. Anita Westergren for valuable collaboration and Docent
Ingvar Andersson for positive criticism;
Mrs. Agnes Ryberg for technical assistance during the experimental and clinical part;
Mrs. Anita Burnett and Mrs. Gail Åkerman for technical assistance of the experimental part, Miss Lisbeth Bäckström, Miss Flora Cesare, Miss Agneta Edeborg, Miss Siv Granelli, Mrs. Anette Holmén and Miss Ulla-Lena Ringquist for technical assistance of the clinical part and Mrs. Marie-Louise Tengryd at the Department of Vascular Surgery for kind co-operation;
Mr. Lars Jansson, Miss Gunilla Scheller and Mrs. Lottie Wulff for drawing the pictures;
Mr. Rune Ohlsson and Miss Jane Rosensköld for phototechnical assistance;
Mrs. Brabo Flakmert for skilful secretarial help;
Mrs. Gail Åkerman for revising the English text;

Nyegaard & Co., Oslo, for supplying C29, Cpd 593, iohexol and metrizamide and Laboratoire Guerbet for supplying ioxaglate.

The investigation was supported by grants from:
The Swedish Medical Research Council, project No. 3483 and the Faculty of Medicine, University of Lund.

Printed in offset
Allmänna Sjukhuset
Malmö 1982



"Hae ä gjortt nu mor"

Bevingat uttryck fällt av Njurunda-soldaten Bogg-Hans, förfader till författaren, när denne kom hem från kriget på själva julkvällen efter 27 års bortavaro, därav 8 år med Karl XII i Ryssland och 13 år i fångenskap.



"Since the reported incidence of contrast media reactions is relatively low, their importance is generally ignored by radiologists. They are, however, not ignored by the patients to whom they cause considerable discomfort. Notably, lower limb arteriography is often extremely painful. Since the patients usually do not publish and since our methodology is better suited to follow other parameters, this problem is usually omitted from the list of contrast media vices."

Sovak et coll. (8).

This thesis is based on the following papers:

- I. NYMAN U. and ALMEN T.:
ARTERIAL AND VENOUS BLOOD PRESSURE AND BLOOD FLOW FOLLOWING
FEMORAL ANGIOGRAPHY WITH A NEW NON-IONIC CONTRAST MEDIUM.
An experimental investigation in dogs.
Acta Radiol. Diagnosis 19 (1978), 1025.
- II. NYMAN U., ALMEN T. and LANDTMAN U.:
EFFECT OF pH, BUFFER AND OSMOLALITY OF DIFFERENT CONTRAST
MEDIA ON AORTIC BLOOD PRESSURE IN THE RABBIT.
Acta Radiol. Diagnosis 21 (1980), 679.
- III. NYMAN U., ALMEN T. and LANDTMAN M.:
EFFECT OF CONTRAST MEDIA ON FEMORAL BLOOD FLOW.
Comparison between non-ionic and ionic monomeric and mono-
acidic dimeric contrast media in the dog.
Acta Radiol. Suppl. 362 (1980), 43.
- IV. NYMAN U and ALMEN T.:
EFFECTS OF CONTRAST MEDIA ON AORTIC ENDOTHELIUM.
Experiments in the rat with non-ionic and ionic monomeric
and monoacidic dimeric contrast media.
Acta Radiol. Suppl. 362 (1980), 65.
- V. NYMAN U., NILSSON P. and WESTERGREN A.:
PAIN AND HEMODYNAMIC EFFECTS IN AORTOFEMORAL ANGIOGRAPHY.
Clinical comparison of iohexol, ioxaglate and metrizamide.
Accepted for publication in Acta Radiol. Diagnosis.

The papers will be referred in the text to their Roman numerals

I - V.

CONTENTS

INTRODUCTION	7
Aortofemoral angiography	7
General principles of contrast media	8
Currently used ratio 1.5 contrast media	8
Ratio 2.0 contrast media	11
First generation of ratio 3.0 contrast media	11
Second generation of ratio 3.0 contrast media	12
AIM OF THE PRESENT INVESTIGATION	14
SUMMARIES OF MATERIAL, METHODS AND RESULTS	15
Arterial and venous blood pressure and blood flow following femoral angiography with a new non-ionic contrast medium. An experimental study in dogs (I).	20
Effect of pH, buffer and osmolality of different contrast media on aortic blood pressure in the rabbit (II).	22
Effects of contrast media on femoral blood flow. Comparison between non-ionic and ionic monomeric and monoacidic dimeric contrast media in the dog (III).	24
Effects of contrast media on aortic endothelium. Experiments in the rat with non-ionic and ionic monomeric and monoacidic dimeric contrast media (IV).	26
Pain and hemodynamic effects in aortofemoral angiography. Clinical comparison of iohexol, ioxaglate and metrizamide (V).	27
GENERAL DISCUSSION	33
GENERAL SUMMARY AND CONCLUSIONS	43
REFERENCES	45
Paper I	
Paper II	
Paper III	
Paper IV	
Paper V	

INTRODUCTION

Angiography of the lower limbs was originally described by BROOKS 1924 (1), who used an aqueous solution of sodium iodide as contrast medium. Intra-arterial injection of concentrated solutions of sodium iodide was extremely painful, gangrenes were observed and the systemic toxicity was high (2, 3). Though the toxicity of intravascular contrast media has decreased and the angiographic technique improved since that time, the patients' discomfort is still considerable and complications do occur.

The present investigation has been performed parallel with the development of new intravascular contrast media with the intention of minimizing the risk for complications and to reduce the patients' discomfort during angiographic examinations. The interest was focused on vascular effects and pain caused by contrast media during aortofemoral angiography.

Aortofemoral angiography

Aortofemoral angiography is most commonly performed in patients with arterial obliterative disease. It is essential for proper choice of the surgical method when reconstructive vascular surgery is considered in these patients. The examination gives information about the distribution and extent of vascular stenoses and occlusions, the patency of collateral vessels and the properties of vessels that might be used for distal anastomosis of grafts. At present about 200 aortofemoral angiographies per year are performed among the 230.000 inhabitants in Malmö.

At Malmö General Hospital the examination implies introduction of a pigtail polyethylene catheter with multiple sideholes into the femoral artery under local anesthesia according to the technique described by SELDINGER 1953 (4). The catheter is then advanced to the abdominal aorta. Multiple injections of 30 to 50 ml of a contrast medium solution containing 280 mg iodine/ml at a rate of 12 to 20 ml/s are performed to visualize the abdominal aorta, pelvic arteries and the arteries of the lower limbs. Complications may result from the catheterization procedure as well as from toxic effects of contrast media.

The catheterization procedure may cause hematoma at the site of puncture, thromboembolic events and trauma to the vessel wall by subintimal passage of guide wires and catheters (5, 6). Furthermore subintimal injections of the contrast medium may occur. In order to decrease these complications the angiographic technique has continuously been refined, and less traumatic catheters and guide wires have been developed.

A contrast medium solution may produce local side effects in the area distal to the site of injection which is exposed to a high concentration of the solution. Adverse effects on organs remote from the site of injection, although exposed to a more dilute solution, may also occur.

General principles of contrast media

An ideal contrast medium for aortofemoral angiography should provide:

1. maximum attenuation of X-rays
2. biological inertness for the patient's safety
3. chemical stability to obtain sterile solutions that tolerate storage.

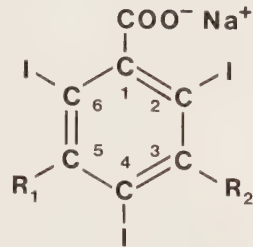
The best compromise for fulfilling these requirements has to date been achieved with iodine atoms incorporated into an aromatic nucleus. Adequate angiographic demonstration of arteries requires high concentration of iodine in solution. The currently used contrast media are injected at a concentration of 280 to 370 mg I/ml which corresponds to a weight/volume concentration of contrast medium in solution of 60 to 76 per cent (g contrast medium/100 ml). A prerequisite for such high concentrations is that the compound is highly water soluble. In addition the viscosity of the solutions must be low enough to permit rapid injection through narrow catheters to obtain a high contrast medium concentration in the vessels.

Currently used ratio 1.5 contrast media

Today the most commonly used intravascular contrast media are salts of tri-iodinated benzoic acid (Fig. 1) such as diatrizoate (Hypaque, Renografin and Urografin), iothalamate (Conray), metrizoate (Isopaque and Triosil), iodamide (Uromiro and Uromiron) and ioxithalamate (Vasobrix and Telebrix).

These compounds are often referred to as ionic because they dissociate into ions in solution, and monomeric since they contain one iodinated aromatic ring.

Fig. 1. Schematic chemical structure of currently used ionic monomeric contrast media.



The radiopaque molecule is thus based on a benzene ring in which three hydrogen atoms have been substituted with three iodine atoms (I) firmly attached to carbon atoms (C) in positions 2, 4 and 6. To achieve high water solubility and low toxicity the remaining hydrogens are replaced with one salt forming carboxyl group ($\text{COO}^- \text{H}^+$) at position 1 and two other radicals (R_1 and R_2) at positions 3 and 5. In solution each molecule of the salt dissociates into one cation (sodium, calcium, magnesium and/or meglumine) and one anion (the iodinated benzoate). This results in a ratio between the number of iodine atoms/number of particles in an ideal solution of $3/2 = 1.5$. The iodine atom/particle ratio determines the radiopacity relative to the osmolality of a contrast medium solution.

Solutions of ratio 1.5 contrast media used in angiography are hypertonic relative to plasma. Adverse effects can be attributed to hypertonicity as well as to chemotoxicity of the contrast medium molecules and other components in the solutions (7, 8). The development of contrast media from sodium iodide to the currently used ionic monomers has resulted in a decrease in systemic toxicity by a factor of 10 (9) as evaluated by intravenous LD_{50} in animals, i.e., the dose required to kill 50 per cent of the animals. The osmolality of the solutions has in iodine equivalent concentrations decreased by a factor of 3 (Fig. 2). The decreased toxicity has, however, to some part been counteracted by the con-

tinuously increasing amounts used to obtain proper examinations. BROOKS used 10 ml while the amount used today often reaches 200 ml with a maximum at Malmö General Hospital of 300 ml.

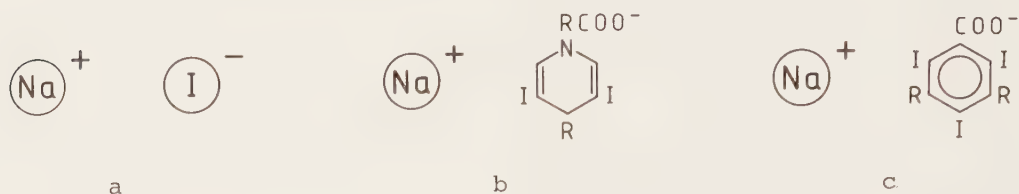


Fig. 2. Iodine atom/particle ratio of a) sodium iodide, 0.5, b) a previously used di-iodinated pyridone derivate, 1.0 and c) a tri-iodinated ionic monomeric compound, 1.5.

At a concentration of 280 mg I/ml the ratio 1.5 contrast media (0.74 mol contrast medium/l) have an osmolality about 5 times that of human plasma. A rapid injection of such a highly concentrated and hypertonic solution will to a large extent replace the blood for a short period in the vessels and cause toxic effects in the area distal to the site of injection. During aortofemoral angiography such effects may result in:

1. Pain which is experienced by most patients and especially those with markedly reduced flow of blood/contrast medium.
2. Decrease in peripheral vascular resistance (10-13) reflected as an increased local blood flow and a fall in systemic blood pressure. Elderly patients with cardiovascular disease may have a decreased ability to compensate for such a fall in blood pressure, which in turn may lead to ischemic complications in remote organs such as the heart and brain.
3. Endothelial damage (14-17) has been demonstrated in animal experiments. These injuries might initiate formation of thrombi.
4. Spinal cord lesion (18-21) with paraplegia, which however is a rare complication of abdominal aortography.

One approach to further increase the tolerability of contrast media has been to reduce their osmolality by decreasing the number of particles in solution without decreasing the iodine content, i.e., to increase the iodine/particle ratio.

Ratio 2.0 contrast media

The synthesis of compounds in which two tri-iodinated anions were linked together by a side chain to form a di-acidic (two carboxyl groups) dimer (two aromatic rings) resulted in contrast media with an iodine atom/particle ratio of 6/3 (Fig. 3).

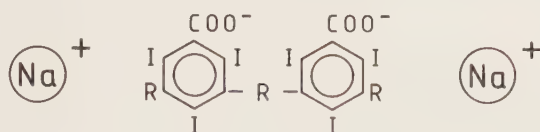


Fig. 3. Principle chemical structure of ratio. 2.0 contrast medium.

The ratio 2.0 compounds produced less sensation of pain (22), less reduction of peripheral vascular resistance (10) and less endothelial damage (23) than the ratio 1.5 media.

First generation of ratio 3.0 contrast media

ALMÉN, 1969, (24) suggested the synthesis of non-ionic contrast agents by exchanging the carboxyl group of a conventional ionic monomeric contrast medium into a radical which does not dissociate into ions in solution but still contributes to water-solubility. A monomeric compound of this non-ionic type with a ratio of 3.0 should in iodine equivalent concentrations have an osmolality half that of ratio 1.5 contrast media (Fig. 4).

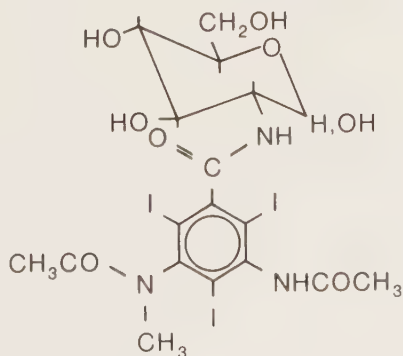


Fig. 4. Chemical structure of metrizamide, which is a glucose-amide of metrizoic acid.

The first clinically available non-ionic monomer, metrizamide (Amipaque), had at high iodine concentrations a measured osmolality that was only one third of that of an ionic monomeric compound. This is explained by aggregation of metrizamide molecules in the solution resulting in a number of separate particles lower than the theoretical one.

The intravenous toxicity of metrizamide is approximately half that of currently used ionic monomers (25). When used in aorto-femoral angiography the sensation of pain has been markedly less than with ratio 1.5 media (26, 27). It also produces significantly less decrease in vascular resistance than both ratio 2.0 and 1.5 agents (28, 29) and less endothelial damage than the ratio 1.5 but similar to that of the ratio 2.0 compounds (23, 30).

The presence of a glucose group in metrizamide makes the solution unstable at sterilization by autoclaving at physiological pH. Autoclaving is better tolerated at a lower pH, but acidity might per se have resulted in toxic consequences. Therefore it was decided to sterilize metrizamide by filtration and deliver it as a freeze dried substance. Before use this dried powder is dissolved in bicarbonate buffer at physiological pH. Partly because of the sterilization procedure metrizamide is an expensive product. Two hundred ml of metrizamide, an amount often used in aortofemoral angiography, will cost about 3.000 Sw. Crs. compared with 100 Sw. Crs. for metrizoate (Isopaque Cerebral, 280 mg I/ml). Metrizamide has not been used routinely in aortofemoral angiography due to the cost and the inconvenience of dissolving it prior to use.

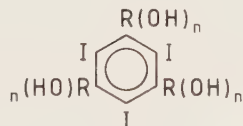
Second generation of ratio 3.0 contrast media

To overcome the disadvantages with metrizamide a number of substances were developed by various companies with the goal of finding a water-soluble contrast medium which tolerates autoclaving and has the same low osmolality and toxicity as metrizamide. These new ratio 3.0 contrast media have been synthesized according to two different principles.

1. Non-ionic monomeric compounds based upon the benzene ring with three iodine atoms per molecule and multiple hydroxyl groups

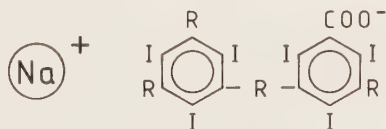
attached to the side chains to provide for water solubility (Fig. 5).

Fig. 5. Schematic chemical structure of second generation of non-ionic contrast media.



2. Mono-acidic dimeric compounds in which one of the two carboxyl groups of a di-acidic dimer has been exchanged for a non-dissociating radical. One molecule of such a salt will in solution dissociate into one cation and one anion containing six iodine atoms, i.e., a ratio of 6/2 (Fig. 6).

Fig. 6. Schematic chemical structure of a mono-acidic dimer.



The first ratio 3.0 contrast medium of the second generation that became available for our research was the non-ionic monomer C29. The stability of this compound towards sterilization with autoclaving was, like that of metrizamide, improved when the solution was buffered at an acidic pH.

During the work with different buffering systems it was later found that TRIS buffer, tris (hydroxymethyl) - aminomethane, had a special property during autoclaving (Swed. pat. appl. 7905830-1). When a non-ionic contrast medium was dissolved at physiological pH in TRIS, the pH of the solution decreased to about 5 during the heating procedure, thereby improving the stability of the compound towards autoclaving. When the sterilization was completed and the temperature of the solution fell, its pH returned to the physiological range. Thus non-ionic contrast media dissolved in TRIS could both tolerate autoclaving and be delivered as a solution at physiological pH.

During this period the monoacidic dimer ioxaglate was released for our investigations. C29 was later discarded for clinical trials

due to the appearance of crystals in the supersaturated solutions, which also happened to Cpd 593, another second generation non-ionic monomer. Instead the non-ionic monomer iohexol, containing one more hydroxyl group than C29, became available.

AIM OF THE PRESENT INVESTIGATION

The aim of the present investigation was to contribute to the improvement of aortofemoral angiographies. For that purpose an experimental and clinical study of second generation of ratio 3.0 contrast media was performed with regard to their vascular and pain producing effects.

The investigation includes:

- I. The effects of injection of second generation of ratio 3.0 contrast media into the aorta and femoral arteries of animals on
 - a. peripheral vascular resistance by recording blood flow and blood pressure, and
 - b. vascular endothelium as assessed with silver staining technique.

The following second generation of ratio 3.0 contrast medium solutions were studied:

1. C29 dissolved in phosphate buffer at physiological and acidic pH
2. C29 dissolved in TRIS buffer at physiological pH
3. Cpd 593 dissolved in TRIS buffer at physiological pH
4. Iohexol dissolved in TRIS buffer at physiological pH
5. Meglumine/sodium ioxaglate (w/w 2/1) at physiological pH

- II. The effects of iohexol and ioxaglate in aortofemoral angiography in man on
 - a. peripheral vascular resistance by recording blood flow and blood pressure, and
 - b. sensation of heat and pain, or any other patient reaction.

SUMMARIES OF MATERIAL, METHODS AND RESULTS

Table 1 gives the nomenclature, molecular weight, iodine content and manufacturers of various contrast media.

Table 2 gives the iodine and substance concentration, osmolality and viscosity of various contrast media. The substance concentration, osmolality and viscosity of the sodium chloride solutions used are also given.

Table 3 gives the molecular weight, mass and substance concentration of the various salts of ionic contrast media used.

The values given in the tables are obtained from the manufacturers.

Figure 7 gives the chemical structure of various contrast media.

Metrizamide (Amipaque) is dissolved in sodium bicarbonate buffer at a substance concentration of 0.6 mmol/l. The substance concentration of sodium phosphate and TRIS buffer in the second generation of ratio 3.0 contrast medium solutions is 0.01 mol/l.

Statistics. Statistical significances were evaluated with Wilcoxon's test for paired differences in paper I - III and V. Mann-Whitney's test for unpaired data was used in paper IV. p-values of 0.05 or less were considered significant except for the observations in paper IV where a p-value of 0.01 or less was used.

Table 1

Nomenclature, molecular weight, iodine content and manufacturers of various contrast media

Trade or experimental name Non-ionic contrast media	Nonproprietary name	Molecular weight*	Iodine content in per cent	Manufacturer
Amipaque	metrizamide	789	48.2	Nyegaard & Co., Oslo
Omnipaque	iohexol	821	46.4	" - "
C29 (Cpd 543)	—	791	48.1	" - "
Cpd 593	—	791	48.1	" - "
Solutrast	iopamidol	777	49.0	Bracco, Milan
Ionic contrast media	acid	salt		
Isopaque	metrizoic	metrizoate	628	60.6 Nyegaard & Co., Oslo
Conray	iothalamic	iothalamate	614	62.0 Astra Meditec, Gothenburg
Urografin	diatrizoic	diatrizoate	614	62.0 Schering AG, Berlin
Hexabrix	ioxaglic	ioxaglate	1269	60.0 Laboratoire Guerbet, Paris

* The molecular weight for the ionic media are given as their acids.

Table 2

Concentration, osmolality and viscosity of various solutions

Contrast media and sodium chloride	Iodine conc. mg/ml	Subst. conc. mol/l	Osmolality mol/kg H ₂ O	Viscosity mPa·s	
				20°	37°
Amipaque	280	0.74	0.43	9.7	5.0
Omnipaque	280	0.74	0.62	8.8	4.8
C29	280	0.74	0.46	7.4	4.1
Hexabrix [*]	280	0.37	0.51 ^{**}	9.3 ^{**}	5.8 ^{**}
Isopaque Cerebral	280	0.73	1.46	7.1	4.0
Conray Meglumine	282	0.74	1.47	6.9	4.0
Urografin 60 %	290	0.77	1.50	7.2	4.0
Amipaque	300	0.79	0.45 ^{**}	12.7 ^{**}	6.2 ^{**}
Omnipaque	300	0.79	0.69	11.6	6.1
Solutrast	300	0.79	0.62	8.8	4.7
Hexabrix [*]	300	0.39	0.55	12.5	6.0
Hexabrix 32 %	320	0.42	0.58	15.7	7.5
Amipaque	370	0.97	0.58	37.0	16.0
Omnipaque	370	0.97	0.98	29.6	13.5
C29	370	0.97	0.62	23.0 ^{**}	10.6 ^{**}
Cpd 593	370	0.97	0.58	23.0	10.8
Solutrast	370	0.97	0.80	18.5	8.6
Hexabrix	370	0.49	0.67 ^{***}	40.0 ^{****}	16.5 ^{****}
Urografin 76 %	370	0.97	2.10	18.5	8.9
Isopaque Coronar	370	0.96	2.15	17.3	8.4
Sodium chloride	-	0.15	0.28	1.0	1.0
" "	-	0.25	0.46	1.0	1.0
" "	-	0.75	1.38	1.0	1.0
" "	-	1.05	1.95	1.0	1.0

* Hexabrix 32 % diluted with distilled water.

** Estimated by interpolation.

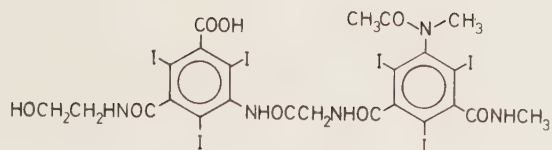
*** Estimated by extrapolation.

**** Estimated by Nyegaard & Co.

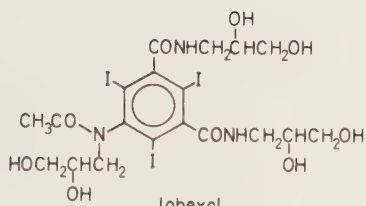
Table 3

Molecular weight and concentrations of the various salts in ionic contrast media

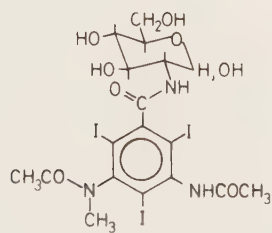
Contrast media	Molecular weight	Mass conc. mg/ml	Subst. conc. mol/l
Urografin 60 %			
sodium diatrizoate	636	80	0.126
meglumine diatrizoate	809	520	0.643
Urografin 76 %			
sodium diatrizoate	636	100	0.157
meglumine diatrizoate	809	660	0.816
Isopaque Cerebral			
calcium metrizoate	1294	11.3	0.0087
meglumine metrizoate	823	591	0.718
Isopaque Coronar			
calcium metrizoate	1294	11.3	0.0087
sodium metrizoate	650	101	0.155
meglumine metrizoate	823	656.5	0.798
Conray Meglumine			
meglumine iothalamate	809	600	0.742
Hexabrix 32 %			
sodium ioxaglate	1291	196.5	0.152
meglumine ioxaglate	1464	393	0.268



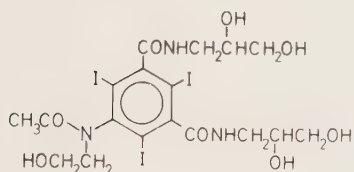
Ioxaglic acid



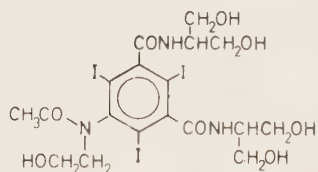
Iohexol



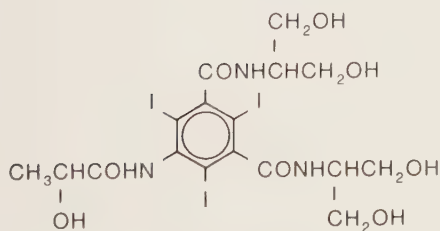
Metrizamide



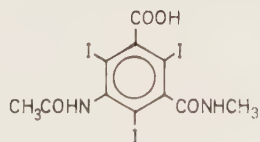
C29 (Cpd. 543)



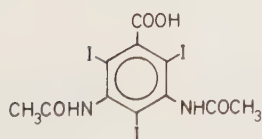
Cpd. 593



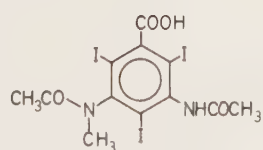
Iopamidol



Iothalamic acid



Diatrizoic acid



Metrizoic acid

Fig. 7. Chemical structure of various contrast media.

ARTERIAL AND VENOUS BLOOD PRESSURE AND BLOOD FLOW FOLLOWING
FEMORAL ANGIOGRAPHY WITH A NEW NON-IONIC CONTRAST MEDIUM.

An experimental study in dogs (I).

Material and methods. Ten mongrel dogs of both sexes were anesthetized with intravenous pentobarbitone and allowed to breathe spontaneously through an endotracheal tube. Three polyethylene catheters were inserted: one into a muscular branch of the left femoral artery for injection of the various solutions, and one into the aorta via the right femoral artery and one into a vein of the left hind leg for blood pressure recordings. Mean blood flow and integrated blood volumes were recorded with a square wave electromagnetic flow meter with the transducer adapted around the surgically exposed left femoral artery proximal to the site of injection. Diatrizoate, metrizamide, C29 dissolved in sodium phosphate buffer and sodium chloride 0.15 mol/l were injected manually, in random order, at two dose levels, (0.1 and 0.2 ml/kg bodyweight) and with a rate of injection of about 1 ml/s. The contrast media had a concentration of 280 mg I/ml. Films were exposed after the contrast medium injections in 5 of the dogs at the lower dose level and in 3 at the higher level.

Results. The contrast medium injections caused an increased blood flow and increased venous blood pressure with a maximum half a minute after the start of injection. Simultaneously aortic blood pressure decreased slightly after injections of diatrizoate, while that occurred only occasionally after the injections of metrizamide and C29. Isotonic sodium chloride produced an increased blood flow but no significant changes regarding aortic and venous pressure. The maximum changes of these parameters and the average increase in blood flow during a 3-min period are illustrated in Fig. 8. At both dose levels diatrizoate caused a significantly higher maximum increase as well as average increase during a 3-min period in blood flow than metrizamide and C29, while there was no significant difference between the two latter compounds. The effect of isotonic sodium chloride on blood flow was significantly less than that of metrizamide and C29 at the higher dose level. At the lower dose level injections of saline generally caused less increase in blood flow than the non-ionic

contrast media though this difference was not statistically significant. The contrast medium concentration in arteries and veins, as evaluated from the films, seemed to be similar for all three contrast media and there was no difference recorded regarding the time of appearance of the contrast media in the femoral vein.

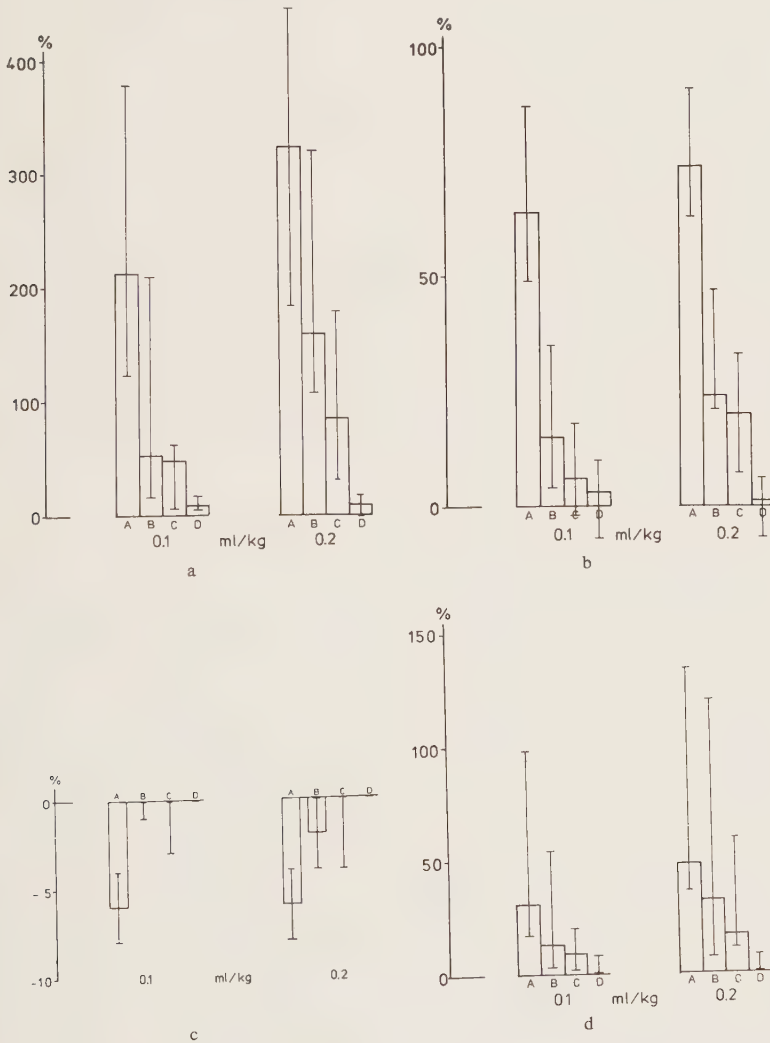


Fig. 8. Changes in blood flow in the left femoral artery, a) maximum increase, b) average increase during a 3-min period. c) Aortic blood pressure, d) venous blood pressure in the left hind leg after injection of the test solutions in the left femoral artery at 2 dose levels, 0.1 and 0.2 ml/kg body weight. Median values, first and third quartiles outlined. A=Urografin, B=Amipaque, C=C29, D=physiologic saline.

EFFECT OF pH, BUFFER AND OSMOLALITY OF DIFFERENT CONTRAST MEDIA
ON AORTIC BLOOD PRESSURE IN THE RABBIT (II).

Material and methods. Forty male rabbits were anesthetized with intravenous pentobarbitone and allowed to breath spontaneously. A polyethylene catheter was inserted via the femoral artery with its tip placed in the distal abdominal aorta for injection of the various solutions and blood pressure recordings. In three groups of animals the effect on aortic blood pressure from variation of pH and buffer of metrizamide and C29 was analyzed and compared with the effects of diatrizoate, metrizoate or iothalamate. In the fourth group the effects of diatrizoate, ioxaglate, metrizamide and C29 were analyzed and compared with solutions of sodium chloride, substance concentration 0.25 and 0.75 mol/l. The contrast media had a concentration of 280 mg I/ml. The various solutions were injected manually, in random order and at a dose of 2 ml. The time of injection was about one second.

Results. All tested solutions except sodium chloride 0.25 mol/l caused a decrease in systolic and diastolic blood pressure which reached a minimum about 10 seconds after the start of injection. The pressure changes returned to normal within one minute. The results are summarized in Table 4. Metrizamide and C29 independent of pH and buffer, and ioxaglate caused a significantly less decrease in aortic blood pressure than the ionic monomeric contrast media. Increasing the acidity of unbuffered or buffered solutions of metrizamide and C29 from physiological pH to pH 5.0 increased the changes in aortic pressure. These differences were statistically significant. When metrizamide and C29 were dissolved in different buffering systems (phosphate, TRIS and bicarbonate) at pH 7.3 or 7.4 no significant difference in response occurred. Sodium chloride 0.75 mol/l and equiosmolal solutions of diatrizoate produced a similar maximum decrease in blood pressure, but the duration of the decrease was significantly shorter after sodium chloride, 16 seconds compared to 25 (median values).

Table 4

Decrease in aortic systolic blood pressure following intra-aortic injection. The figures represent the maximum decrease in systolic pressure after the injection expressed in percentage of the lowest systolic pressure during one min before the injection. Median value and range are given.

	pH	Decrease
Group 1 (n = 12)		
Meglumine/calcium metrizoate (Isopaque Cerebral)	7.2	18.3 (11.3–24.4)
Metrizamide dissolved in diluted hydrochloric acid	5.0	10.3 (6.1–23.5)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	5.0	11.3 (5.1–25.7)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	5.5	7.3 (2.9–12.0)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	6.2	6.4 (2.8–10.5)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	7.4	5.1 (0.0–13.6)
Metrizamide dissolved in sodium bicarbonate buffer 0.0006 mol/l (Amipaque)	7.4	5.8 (0.0–13.1)
Group 2 (n = 10)		
Meglumine iothalamate (Conray Meglumin)	7.3	19.5 (11.4–29.4)
Meglumine/sodium diatrizoate (Urografin)	7.0	18.0 (13.5–31.4)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	5.0	10.5 (1.3–20.0)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	6.0	6.8 (2.7–18.3)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	7.3	5.0 (0.0–10.5)
Group 3 (n = 8)		
Meglumine/calcium metrizoate (Isopaque Cerebral)	7.3	20.1 (13.9–30.0)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	7.3	7.6 (3.0–10.5)
C29 dissolved in TRIS-buffer ((CH ₂ OH) ₃ CNH ₂) 0.01 mol/l	7.4	5.0 (3.1–9.8)
Metrizamide dissolved in sodium bicarb. buffer 0.0006 mol/l (Amipaque)	7.4	6.1 (3.0–9.0)
Group 4 (n = 10)		
Meglumine/sodium diatrizoate (Urografin)	7.0	15.8 (2.3–45.1)
C29 dissolved in TRIS-buffer 0.01 mol/l	7.4	10.0 (0.0–29.5)
Meglumine/sodium ioxaglate	7.4	9.3 (0.0–28.8)
Metrizamide dissolved in sodium bicarb. buffer 0.0006 mol/l (Amipaque)	7.4	7.0 (0.0–28.2)
Sodium chloride unbuffered solution 0.75 mol/l	5.5	16.2 (4.6–50.0)
Sodium chloride unbuffered solution 0.25 mol/l	5.5	0.0 (0.0–1.1)

EFFECTS OF CONTRAST MEDIA ON FEMORAL BLOOD FLOW.

Comparison between non-ionic and ionic monomeric and monoacidic dimeric contrast media in the dog (III).

Material and methods. Twenty mongrel dogs were used in two experimental series with ten in each. The animals were prepared for injection of the various solutions into the femoral artery and blood flow measured according to the technique described in paper I. Aortic blood pressure was recorded in group II. In group I metrizoate, metrizamide, C29 dissolved in TRIS buffer and sodium chloride (0.15, 0.25 and 0.75 mol/l) were injected, and in group II metrizoate, ioxaglate, iohexol and metrizamide. The contrast media had a concentration of 280 mg I/ml. The solutions were injected manually, in random order and at a dose of 0.1 and 0.2 ml/kg bodyweight in group I and at 0.2 ml/kg in group II. The rate of injection was about 1 ml/s.

Results. The time-related changes in femoral blood flow after injection of the various solutions are illustrated in Fig. 9. At both dose levels in group I metrizamide and C29 produced a significantly less increase in blood flow than metrizoate and sodium chloride 0.75 mol/l. There was no significant difference between the two former or between the two latter compounds in this group. In group II no significant difference in blood flow was recorded after injection of metrizamide, iohexol and ioxaglate, and they all caused significantly less changes than metrizoate. The mentioned differences were valid for both maximum increase and average increase during a 3-min period in blood flow. A slight fall in systolic and diastolic blood pressure was noted simultaneously with the increase in blood flow following injection of metrizoate in group II. No obvious changes in blood pressure occurred after the other contrast media.

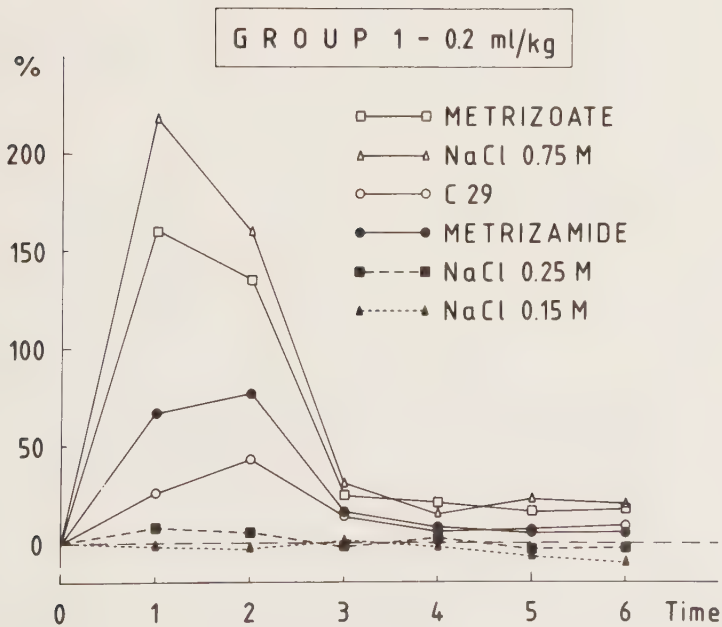
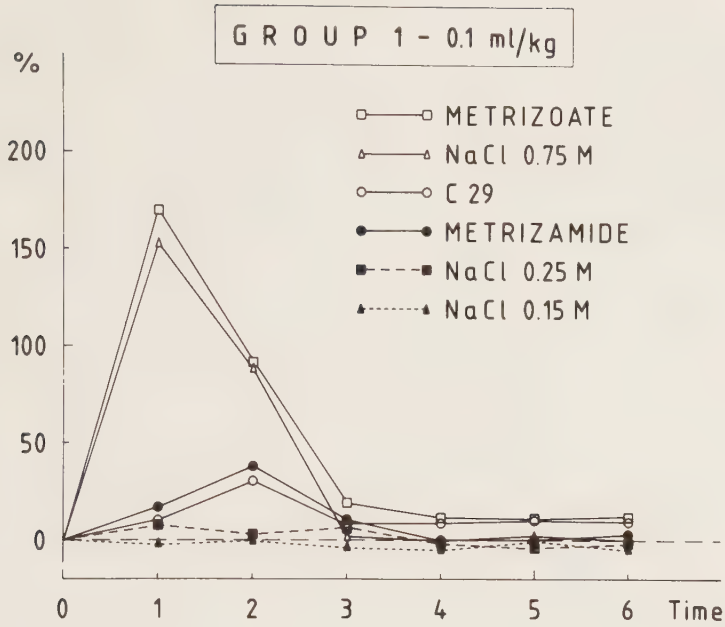


Fig. 9.

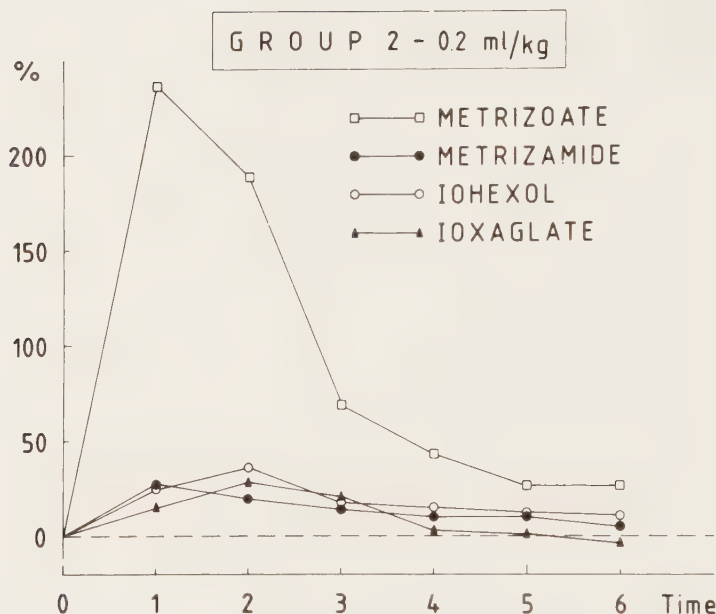


Fig. 9. Changes in average blood flow during 6 consecutive 30-s periods after injection expressed in per cent of the average blood flow during one min before injection (median values).

EFFECTS OF CONTRAST MEDIA ON AORTIC ENDOTHELIUM.

Experiments in the rat with non-ionic and ionic monomeric and monoacidic dimeric contrast media (IV).

Material and methods. One hundred and ten male Wistar rats were anesthetized with ether and intraperitoneal injection of mebumal. A polyethylene catheter was inserted in cranial direction with its tip located in the proximal part of the abdominal aorta, the heart was removed and the thoracic aorta rinsed from blood by an injection of saline. The aortic endothelium was then exposed to the following solutions: 5 ml of one of the test solutions for 5 min, 10 ml isotonic sodium chloride for 1 min, 5 ml silver nitrate 0.25 % (w/v) for 30 s, 10 ml glucose 5.5 % for 1 min and 10 % formalin for 30 min. The thoracic aorta was then opened ventrally and placed with the adventitial side down on a glass

slide, fixated with formalin for 24 h, washed in distilled water for 12 h, dehydrated in graded alcohols during three 5-min periods, cleared with xylene for 30 s and mounted with canada balsam under a cover slip. The specimens were systematically scanned under a light microscope and areas with endothelial injury, characterized by dark parallel stripes running at right angles to the normal endothelial pattern were expressed in per cent of the total area examined. Each solution was tested in 10 rats. The contrast media had a concentration of 370 mg I/ml.

Results. The extent of subendothelial silver staining caused by the various test solutions are illustrated in Fig. 10. The changes found in the specimens perfused with isotonic sodium chloride were significantly less than those found after perfusion with the remaining solutions. Injection of diatrizoate and metrizoate caused the most extensive injuries and the difference noted compared with the other solutions were statistically significant. No major difference was found between solutions of C29 with various pH and buffer, Cpd 593, iohexol, metrizamide, ioxaglate and sodium chloride with a substance concentration of 1.05 mol/l, which is equiosmolal with solutions of diatrizoate and metrizoate.

PAIN AND HEMODYNAMIC EFFECTS IN AORTOFEMORAL ANGIOGRAPHY. Clinical comparison of iohexol, ioxaglate and metrizamide (V).

Material and methods. Forty patients referred for aortofemoral angiography because of obliterative arterial disease were selected and divided into two groups. Patients with poor general condition, diabetes, reduced renal function and lower extremity neuropathy were excluded. Following a lumbar aortography with 30 ml of metrizoate the tip of the angiographic catheter was placed 4 to 5 cm above the aortic bifurcation for the remaining contrast medium injections. The patients in group 1 (N=20) received 45 ml (12 ml/s) of iohexol and metrizamide (300 mg I/ml) in a single blind randomized fashion. Patients in group 2 (N=20) received 50 ml (12 ml/s) of ioxaglate and metrizamide (300 mg I/ml) in a similar way. Any additional injections were performed with metrizoate (280 mg I/ml, 45 ml and 12 ml/s in group 1, and 30 ml and 15 to

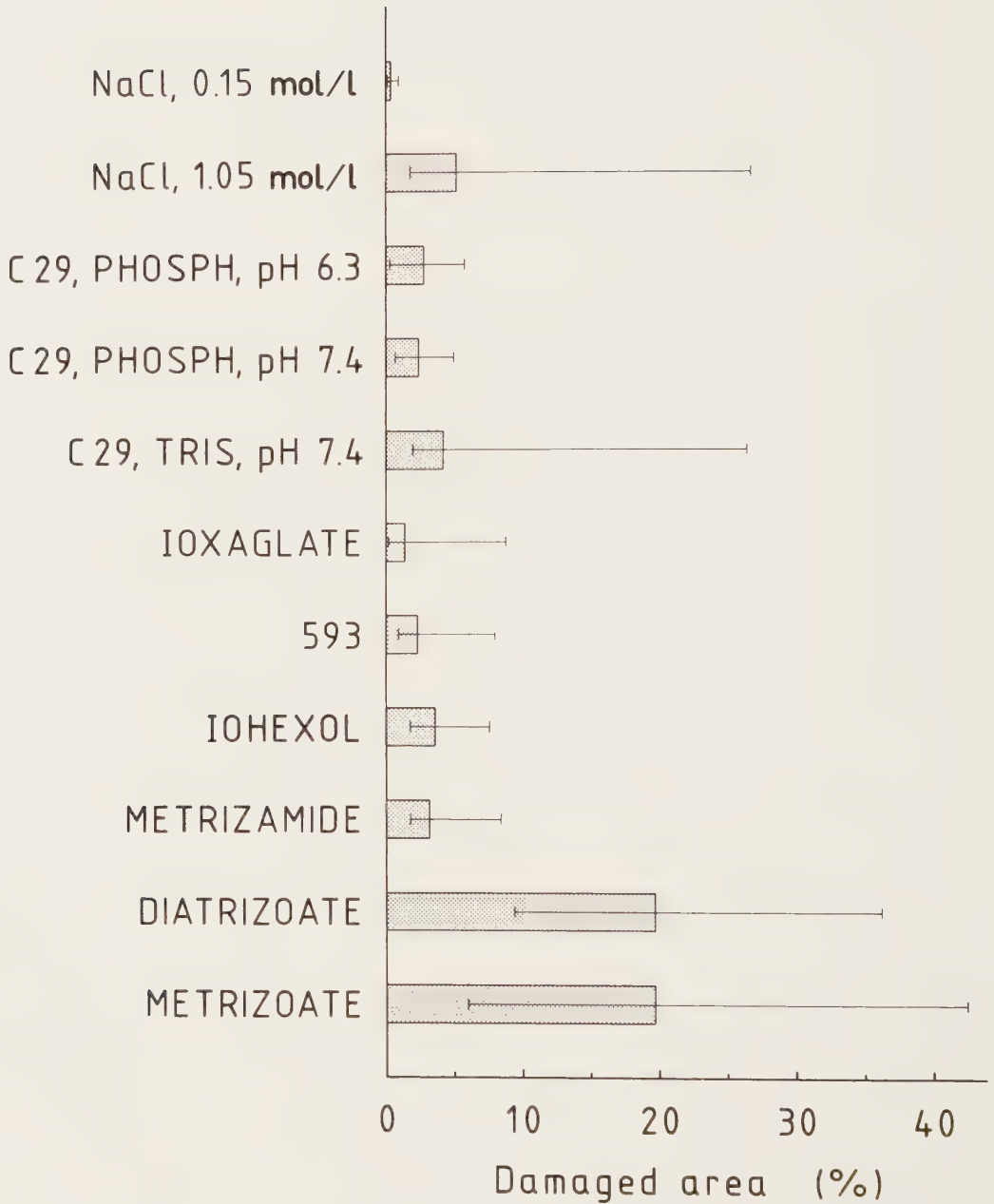


Fig. 10. Extent of endothelial injury caused by the different test solutions. Median value and range are given.

20ml/s in group 2). The degree of heat and pain was marked by the patients on a visual analogue scale after injection of iohexol, ioxaglate, metrizamide and the subsequent injection of metrizoate. Blood flow, mean aortic blood pressure and a precordial ECG were recorded before and for about 3 min after injection of iohexol, ioxaglate and metrizamide in 10 patients without pain at rest in each group. Calf blood flow was recorded with strain gauge plethysmography and mean aortic pressure through the angiographic catheter. Total vascular resistance was defined as the quotient between mean aortic pressure and the sum of blood flow in both calves at each recording.

Results. Patient reactions to the contrast media are summerized in Table 5. The degree of heat was significantly greater after metrizoate than after metrizamide, iohexol and ioxaglate. There was no significant difference between the three latter media. The degree of pain caused by iohexol and ioxaglate did not differ significantly from that of metrizamide. Metrizoate caused significantly more pain than the other three agents. No severe adverse reactions to the contrast media occurred.

Table 5
Number of patients with adverse reactions in
aortofemoral angiography

Contrast medium	Heat	Pain	Nausea	Urticaria
Group 1				
Metrizamide (N=20)	20	3	0	0
Iohexol (N=20)	20	7	1	0
Metrizoate (N=19)	19	18	0	0
Group 2				
Metrizamide (N=20)	20	1	0	0
Ioxaglate (N=20)	20	3	3	1
Metrizoate (N=20)	20	13	0	0

Iohexol, ioxaglate and metrizamide decreased total vascular resistance in all patients as reflected by an increase in calf blood flow and a decrease in aortic blood pressure, which was also accompanied by an increase in heart rate. The decrease in resistance was most pronounced at the 30 and 50 s recordings and returned to preinjection level after about two minutes (Fig. 11). The hemodynamic effects were similar for all three contrast media. On one occasion a short-lasting bradycardia occurred after an injection of iohexol. The diagnostic quality as evaluated from the demonstration of arteries and pathological lesions was the same for metrizamide, iohexol and ioxaglate.

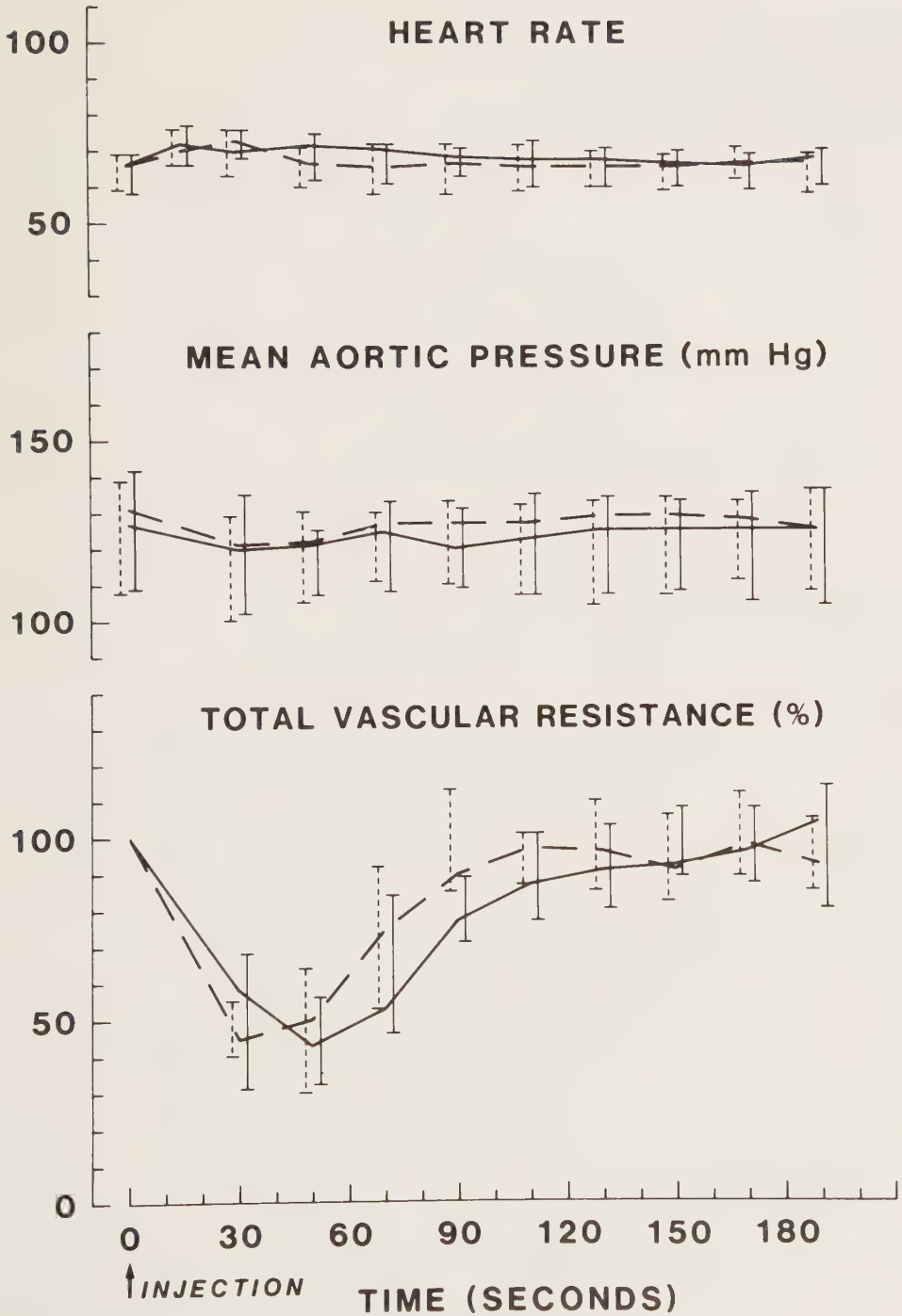


Fig. 11a. Hemodynamic effects of metrizamide (—) and iothexol (---). The curves represent median value with interquartile range outlined.

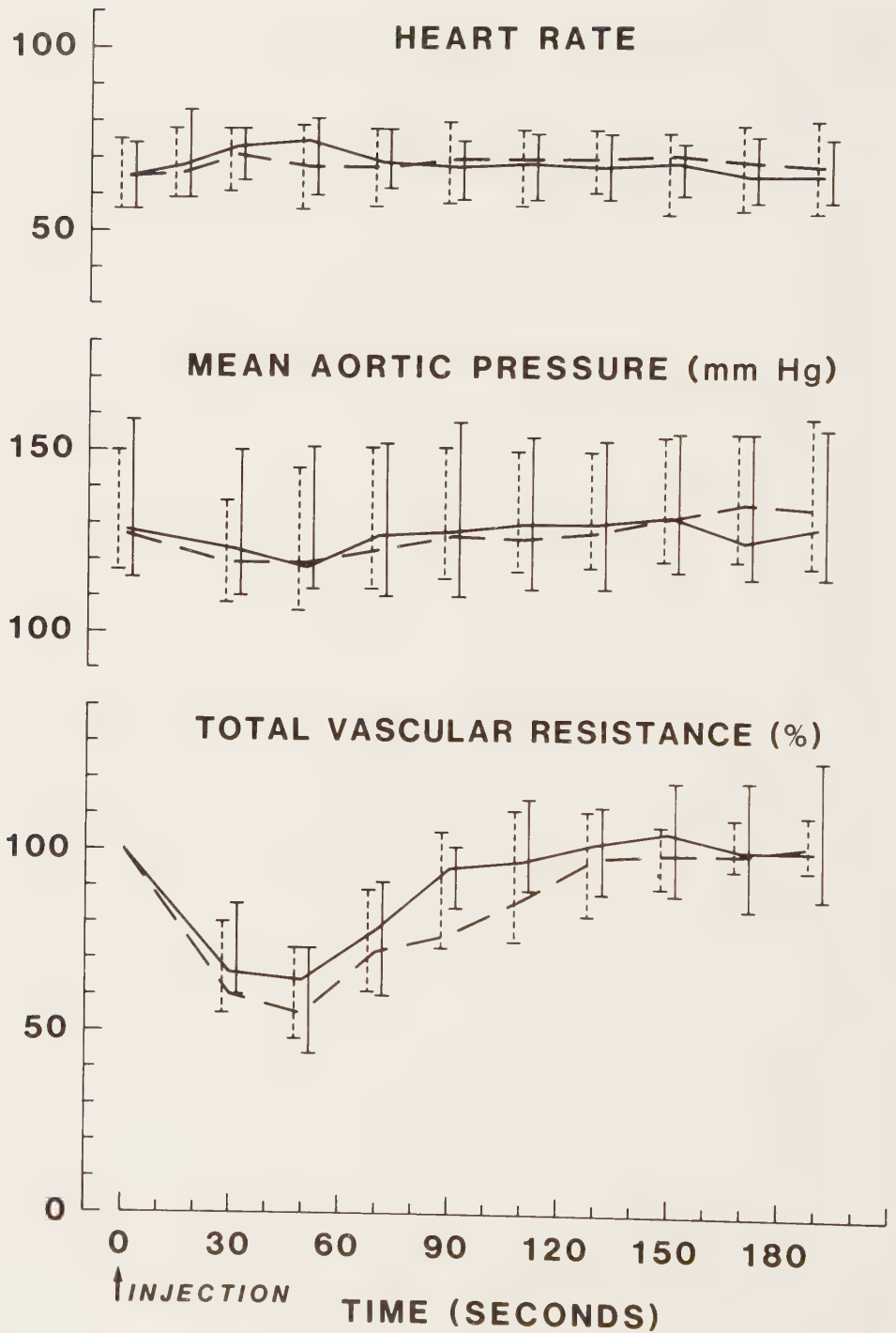


Fig. 11b. Hemodynamic effects of metrizamide (—) and ioxaglate (---). The curves represent median value with interquartile range outlined.

GENERAL DISCUSSION

A contrast medium for aortofemoral angiography should have as low toxic effects as possible in the area distal to the site of injection and on remote organs.

The results of the present investigation indicate that the second generation of ratio 3.0 contrast media cause significantly less decrease in peripheral vascular resistance, less endothelial damage and less sensation of heat and pain than the ratio 1.5 compounds currently used for aortofemoral angiography. The effects of the new generation of low osmolality contrast media seemed to be of the same magnitude as those of metrizamide.

Vascular resistance

The hemodynamic effects of modern ionic monomeric contrast media and other hypertonic solutions when injected into the aorta and extremity arteries are well documented in animal (10, 11, 31-39) and clinical (12, 13, 40, 41) investigations. As demonstrated in paper I the arteriovenous pressure difference decreases and local blood flow increases. Secondary to this an increase in heart rate and cardiac output may be noted. The maximum changes occur during the first minute after injection and have largely subsided 1 to 2 minutes later.

In analogy with Ohm's law, $I = U/R$ ($R = U/I$), the arteriovenous pressure difference ($P_1 - P_2$) is analogous with the potential difference (U) and blood flow (Q) with the current (I), i.e., the resistance (R) to blood flow becomes $R = (P_1 - P_2)/Q$. This means that a decrease in pressure gradient over the peripheral vessels combined with an increased blood flow represent a decreased vascular resistance (R). Hagen-Poiseuille's law about motion of Newtonian liquids in cylindrical rigid tubes states that:

$$Q = K \frac{(P_1 - P_2) \times r^4}{L \times \eta} ; \quad \text{i.e. } R = \frac{P_1 - P_2}{Q} = \frac{I}{K} \times \frac{L \times \eta}{r^4}$$

K = Constant, L = Length of the tube, η = Viscosity,
 r = Radius of the tube

Though the conditions under which Hagen-Poiseuille's law applies are not fulfilled in the human body it can be used for approximative studies of blood circulation (42). Since the quotient $(P_1 - P_2)/Q$ in this formula represents vascular resistance it follows that the resistance is directly proportional to the length (L) of the tube and to the viscosity (η) but inversely proportional to the fourth power of the radius (r) of the tube. The length of any vascular channel is virtually constant for anatomical reasons whereas whole blood viscosity increases after injection of contrast medium solutions (43). Therefore the decrease in vascular resistance caused by contrast media has to be attributed to an increased radius of the vessels which means vasodilatation. The peripheral vascular resistance is regulated mainly by the caliber of the precapillary sphincter vessels, the arterioles (45).

On the basis of earlier investigations as well as the present ones, data about the vasodilatory effect of modern ratio 1.5 contrast media and other hypertonic solutions can be summarized as follows:

1. Injection of the solutions into one femoral artery does not produce any changes in the contralateral femoral vascular bed (28, 32). The effect is not greatly influenced by injection of noradrenaline and antihistamine, spinal anesthesia, chemical blockade of the autonomic nervous system or section of sciatic and femoral nerves (10, 31, 32, 39) though COEL & LASSER (39) found some evidence of a cholinergic effect. Thus vasodilatation is mediated via a local effect of the injected solutions on the peripheral vascular bed and they may act direct on the smooth muscle cell.
2. Solution of sodium chloride isotonic to plasma is virtually without effect compared with that of ratio 1.5 contrast media and other hypertonic solutions (10, 12, 32, 36, I, III). Vasodilatation occurs even if the perfusate does not contain red blood cells (32, 39). Thus the effect noted in the present investigation is unlikely to be due to temperature, volume or rate of injection, or products of hemolysis. Furthermore, neither bradykinin nor histamine need to be present (39).

3. Though some authors state that meglumine salts produce less changes than pure sodium salts (10, 39), there seems to be no major difference between ratio 1.5 contrast media with different anions (10, 11, 34, II) or between these contrast media and equiosmolal solutions of sodium chloride, glucose, mannitol and urea (10, 11, 46, II, III). Thus the most important factor of solutions of modern ratio 1.5 contrast media contributing to vasodilatation seems to be their hypertonicity relative to plasma.

As expected metrizamide, iohexol, C29 and ioxaglate, which in iodine equivalent concentrations have less than half the osmolality of the ratio 1.5 contrast media, caused significantly less vasodilatation than the ratio 1.5 compounds as reflected by the recordings of blood flow (I, III) and blood pressure (II). The results agree with previous animal experiments and clinical trials where metrizamide (28, 29) and ioxaglate (47, 48) have been compared with conventional ionic agents. In a recent study (49) iohexol caused less decrease in aortic blood pressure than diatrizoate during clinical aortofemoral angiography. In one clinical investigation (50) no difference was found between diatrizoate and ioxaglate regarding decrease in blood pressure, but a smaller amount of contrast medium was used than in the other investigations.

It appears from the present (II, III) and earlier experiments by HILAL (10) that sodium chloride solutions in concentrations equiosmolal with the ratio 3.0 contrast media at an iodine concentration of 280 to 320 mg/ml have virtually no effect on vascular resistance. In addition it was found (II) that the hypotensive reaction lasted longer following injection of diatrizoate than after an equiosmolal solution of sodium chloride. This indicates that factors other than hypertonicity of contrast medium solutions may contribute to the effect on vascular resistance and that the relative importance of such factors increases with decreasing osmolality. Such factors might be chemotoxicity of the iodinated molecule, cation composition, viscosity, pH, buffers and chelating agents.

Acetrizoate, a previously used ratio 1.5 contrast medium, was found to be a stronger vasodilator (31) than the ratio 1.5 media used in the present investigation. According to another study (28) metrizamide caused less increase in canine femoral blood flow than Compound 17, a non-ionic medium with an osmolality similar to that of metrizamide. These differences were attributed to a chemotoxic effect of the iodinated organic molecule.

According to microcirculatory studies (51, 52) the passage or ischemic time for contrast medium solutions was longer than for iso- and hypertonic solutions of sodium chloride, which seemed to be related to the viscosity of the solutions. This implies an increased application time for the contrast medium solutions during which they can exert their osmotic effects. In addition the vasodilatation might be partly provoked by ischemia per se.

The slower passage of solutions of contrast medium compared with equiosmolal solutions of sodium chloride through the peripheral vascular bed is in accordance with observations in the present investigation (III). Blood flow as registered by the transducer decreased during injection of all solutions due to its position proximal to the site of injection. When the injection was completed the blood flow returned immediately to the pre-injection level after iso- and hypertonic solutions of sodium chloride but remained decreased an additional five seconds after injection of ratio 3.0 and 1.5 contrast media. SCHRÖDER et coll. (53) obtained similar results after injection of solutions of contrast media and sodium chloride in equiosmolal concentrations into the superior mesenteric artery of the dog. Obviously rigidification of red blood cells induced by hypertonicity (44) causing blockade of capillaries (54) as well as increased whole blood viscosity (43) cannot explain the transient decrease in blood flow. Instead it seems to be related to the viscosity of the solutions.

It is known that solutions both on the acid and alkaline side of the physiological range cause vasodilatation. KESTER et coll. (55) found that buffered solutions of sodium chloride at at low pH decreased vascular resistance but unbuffered solutions did not.

Contrary to this the present (II) and previous results (56) indicate that increasing the acidity of buffered as well as unbuffered solutions of non-ionic contrast media to pH 5.0 increased the fall in blood pressure, though it was still less than the fall produced by ratio 1.5 contrast media. No differences existed between unbuffered and buffered solutions of metrizamide at pH 5.0 (II). These diverging results might be explained by the high viscosity of the contrast medium solutions which delays their mixing with blood and thereby the neutralization of the acidic solution. Variation of buffer (TRIS, phosphate and bicarbonate) in metrizamide and C29 solutions did not cause any differences in hypotensive reactions (II).

From the present series (I, II, III, V) and another experimental (57) and one clinical investigation (58) it seems that the vasodilatory properties of the presently available ratio 3.0 contrast media including the non-ionic monomer, iopamidol (Solutrast, Bracco, Milan) are of the same magnitude in concentrations ranging from 280 to 320 mg I/ml. However, at higher iodine concentrations their vasodilatory effect might differ since the difference in osmolality between the ratio 3.0 agents increases with increasing concentration (Table 2). At a concentration of 370 mg I/ml the osmolality of metrizamide is 60 per cent of that of iohexol.

With regard to the principle of a low viscosity to permit fast injections iopamidol has about the same viscosity as the ratio 1.5 contrast media used in the present investigation. The viscosity of iohexol, metrizamide and ioxaglate is higher especially at a concentration of 370 mg I/ml (Table 2).

Endothelial damage

Silver staining of vessel walls is an old method to disclose injury to vascular endothelium and has also been used for evaluation of contrast medium induced endothelial damage (14-17). Desquamation of endothelial cells and increased permeability permit the silver nitrate solution to penetrate and stain subendothelial structures. With the development of less toxic contrast media the application time has been increased from earlier 1 min to

the present 5 min in order to demonstrate injuries (59). Previous investigations in rats have demonstrated that metrizamide caused significantly less subendothelial silver staining than ratio 1.5 contrast media (30, 59). In the present series (IV) also the second generation of ratio 3.0 contrast media independent of the pH and buffers used were less harmful to rat aortic endothelium than the ionic monomers. The difference noted may partly be explained by the difference in osmolality.

The extent of contrast medium induced endothelial damage reported by RAININKO (60, 61) was about a factor ten less than in the present investigation and in previous reports from this laboratory (23, 30, 62). The reason for this marked difference is not known. It might be ascribed to some difference in methodology or varying sensitivity of the endothelium of different strains of animals. RAININKO (60) also found that diatrizoate was as harmless as metrizamide which is not in agreement with the present and a previous report (59).

No significant difference was found between the ratio 3.0 contrast media regarding their endothelial damaging effect, despite variation of pH and buffer and the differences in osmolality at a concentration of 370 mg I/ml. Moreover sodium chloride in concentration equiosmolal with the ratio 1.5 contrast media had an injurious effect similar to that of the ratio 3.0 agents. This indicates that chemotoxicity of various contrast media plays an important role in causing endothelial damage, which is in accordance with previous investigations where the silver staining technique has been used (14, 17, 23, 61). A chemotoxic effect of contrast medium solutions in addition to the osmotic has also been documented on vascular endothelia in different regions such as blood brain barrier (63, 64), glomeruli of the kidney (65, 66) and hamster cheek pouch (67). According to RAININKO (61) the threshold of injuring hypertonicity on silver stained rat aortic endothelium was at the level of 1.5 mol/kg H_2O .

In a recent report, GOTTLÖB (68) considered silver lines beneath a preserved endothelial pattern as being artefacts caused by dehydration of the vessel wall from the hypertonic contrast

media. According to GOTTLOB injection of solution of silver nitrate then rehydrates the wall and as a result of the rehydration silver nitrate penetrates into the media. The subendothelial silver staining was prevented if the specimens were rehydrated with Ringer solution for 3 minutes before silver staining. It must be questioned, however, whether or not these artefacts actually represent hypertonic injury to the endothelium, though reversible, a phenomenon also observed in the blood brain barrier (64).

The results obtained with the silver staining technique and the knowledge that thrombi tend to form on damaged endothelium, correlate with the clinical observation that the risk for thrombosis after phlebography of the lower limbs is less when metrizamide is used instead of ratio 1.5 contrast media (69-71). Though the 5 minutes application time of contrast media in the experimental series may resemble the situation in clinical phlebography, this time is considerably shorter during arteriography. Furthermore thromboembolic events during angiographic procedures are generally ascribed to clot formation on catheters and vessel trauma at the puncture site. However, MAY & NISSEL (72) reported an incidence of 1.7 per cent occlusions of stenotic vessels or increased extension of already present occlusions within eight days after 2000 translumbar aortographies. Van ANDEL (73) observed six patients where occlusions had developed in stenotic areas within two months after aortofemoral angiography. Both authors regarded the contrast medium as a possible contributing factor to the thrombotic occlusions. Repeated injections of contrast media combined with slow circulation in patients with arterial obliterative disease will prolong the duration of action of the contrast media. Disturbance in the normal laminar flow pattern at the site of stenosis resulting in turbulence may also make the endothelium more vulnerable to contrast medium.

Pain sensation

The pain caused by the currently used ionic monomeric contrast

media during aortofemoral angiography is often a great discomfort to the patient and may also result in motion unsharpness of the images. Though the degree of pain often parallels the degree of vasodilatation, these effects do not appear to be causally inter-related, but rather separate effects of the hypertonicity of ratio 1.5 contrast media (74). Meglumine salts have been considered less painful than sodium salts (74, 75).

In order to reduce the pain during aortofemoral angiography intra-arterial injection of lidocaine and premedication with various drugs (76-79), and even general anesthesia (80) have been used. The effectiveness of lidocaine in reducing pain has been disputed (81) and the use of general anesthesia implies an increased risk for the patients (82, 83).

Several clinical investigations, as well as the present one (V), have shown that the ratio 3.0 contrast media such as ioxaglate, metrizamide, iothexol and iopamidol have markedly reduced the heat and pain sensations compared with ratio 1.5 media (26, 27, 48-50, 84-89). In one investigation (90) ioxaglate was found to cause less pain than diatrizoate mixed with lidocaine.

According to the present (V) and other investigations (58, 91, 92) no major difference in the pain producing effect has been found between ioxaglate, metrizamide, iothexol and iopamidol. Following intrafemoral injection of metrizamide and iothexol in the unanesthetized rat no changes in behaviour indicating pain were observed (93). The difference in degree of pain found by van WAES (94) between metrizamide and ioxaglate, to the disadvantage of the latter, occurred when more selective angiographies were performed.

Spinal cord damage

In a survey of complications of 13.207 abdominal aortographies, McAFEE 1957 (95) found an incidence of 0.22 per cent of spinal cord damage resulting in paraplegia and in some cases even in the patient's death. There seems to have been a relatively higher incidence of such lesions when the more toxic ratio 1.5 medium acetrisoate, was used (6, 21, 96).

The spinal cord is inter alia supplied by a number of branches from intercostal, lumbar and internal iliac arteries (97). Spinal cord damage has been attributed to the combined effects of the neurotoxicity of the contrast agent and a decreased spinal cord circulation (18, 98, 99). The latter may be secondary to effects of the contrast medium on red blood cells. Any procedure that increases the dose, concentration or contact time of the contrast agent to the spinal cord increases the risk of damage, e.g., the injection of contrast medium above an occluded segment of the aorta, unintentional placement of the tip of the catheter or a side-hole in or close to the origin of an artery supplying the spinal cord. Even after satisfactory positioning of a curved catheter tip in the aorta before injection, the injection pressure may open the curve and place the tip in a lumbar artery (100).

The risk for spinal cord lesions might be less with iohexol and ioxaglate than with ionic monomers as the rigidification of erythrocytes decreases with decreasing osmolality of the contrast medium solutions (101). Furthermore the effect of iohexol and ioxaglate on the blood brain barrier is far less than that of the ionic monomeric compounds and comparable to the effect of metrizamide (102, 103). Iohexol seems to be better tolerated than metrizamide after application in the subarachnoid space while ioxaglate is less tolerated than metrizamide (93, 102, 104).

Adverse effects on remote organs

The systemic toxicity of contrast media is very low compared with most other drugs in medicine when the amount tolerated is expressed in g or mmol/kg body weight. However, the dose of a ratio 1.5 contrast medium which a diseased elderly patient might receive during approximately one hour in an aortofemoral angiography is 1.0 to 1.5 g I/kg (2.6 to 3.9 mmol/kg). This dose is 10 to 30 per cent of the acute intravenous LD₅₀ in healthy young animals, which varies between 5 to 10 g I/kg for ratio 1.5 agents (9).

Adverse systemic effects of contrast media include disturbances in the respiratory, cardiovascular and cerebral functions, skin manifestations as well as unspecific symptoms such as nausea and

vomiting (105). SHEHADI and TONIOLI (106) reported an incidence of adverse effects of 2.76 per cent in 27.700 aortographies and other angiographies excluding angiocardiology and cerebral angiography. The incidence of severe reactions was 0.14 per cent and included one fatal complication. Following intravenous injection side effects have been reported to occur in 5 to 8 per cent of the patients (107). Though severe and even fatal reactions have occurred after the injection of only a few ml of a contrast medium solution, there appears to be a dose response relationship for such adverse effects (107).

The acute intravenous toxicity in mice of ioxaglate (108) and metrizamide (25) was found to be half that of ratio 1.5 contrast media. The toxicity of iohexol was found to be even lower - about 20 per cent below that of metrizamide (109). In addition the binding to plasma proteins, the inhibition of lysozymes and the release of histamine were all less for iohexol than for ioxaglate (110). If the hypothesis is valid that adverse reactions to contrast media are directly related to these parameters iohexol should be better tolerated than ioxaglate (110).

In the last decade an increasing number of renal failure induced by contrast media after both intravenous and intra-arterial injection have been reported (111). Advanced age, pre-existing renal insufficiency, diabetes and dehydration are among the risk factors. The pathogenesis has not been established though mechanisms such as contrast medium induced changes in renal hemodynamics, direct tubular toxicity, deformation of red blood cells and intratubular obstruction by urinary protein precipitate have been discussed. Iohexol and ioxaglate may have a potential advantage in this respect as renal hemodynamic changes are related to the osmolality of a contrast medium solution (112) and these media cause less morphological changes of red blood cells (110) and less postangiographic proteinuria (113, 114) compared with both metrizamide and ionic monomers. However, this advantage might be counteracted by the fact that ratio 3.0 contrast media are more concentrated in the urine than ratio 1.5 agents (115) which might tend to increase their toxic effects on tubular cells. In fact metrizamide caused the same increased mitotic rate in tubular

cells as metrizoate (116).

Intravascular injection of hypertonic contrast media may result in increased circulating blood volume (117) and decreased colloid oncotic pressure (118) predisposing to pulmonary edema (118, 119), especially in patients with cardiovascular disease. The ratio 3.0 contrast media cause less increase in blood volume than the ratio 1.5 media (117).

GENERAL SUMMARY AND CONCLUSIONS

Compared with currently used ratio 1.5 contrast media (diatrizoate, iothalamate and metrizoate), injections of second generation of ratio 3.0 contrast media into the aorta and femoral arteries caused significantly

1. less decreased systemic blood pressure and less increased local blood flow, i.e., less decreased peripheral vascular resistance (C29, iohexol and ioxaglate),
2. less endothelial damage as evaluated with a silver staining technique on rat aorta (C29, Cpd 593, iohexol and ioxaglate) and
3. less sensation of heat and pain as evaluated from the patient markings on a visual analogue scale (iohexol and ioxaglate).

The effects of second generation of ratio 3.0 contrast media were similar to those of the first generation (metrizamide).

Contrast medium solutions for aortofemoral angiography should have an osmolality and a pH close to that of human plasma in order to minimize the fall in blood pressure, endothelial damage, and sensation of heat and pain. The choice of buffer (phosphate, TRIS and bicarbonate) in order to give the non-ionic contrast media a proper pH seems to be of minor importance.

The effects of ratio 3.0 contrast media on vascular resistance and endothelium, might be explained by chemotoxicity of the iodinated molecule. The high viscosity of contrast medium solutions tends to increase their contact time with the vessel wall

which might increase the effect of possible toxic factors such as osmolality and chemotoxicity.

The ratio 3.0 contrast media iohexol and ioxaglate seem to be well suited for aortofemoral angiography as they significantly reduce the local side effects and have a lower general toxicity than currently used ratio 1.5 contrast media, provided that their cost becomes tolerable. Iohexol and ioxaglate are supplied as sterile solutions and are as easy to handle as solutions of ratio 1.5 media. With the use of iohexol and ioxaglate intra-arterial lidocaine or general anesthesia is not indicated for routine aortofemoral angiography.

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ARTERIAL AND VENOUS BLOOD PRESSURE AND BLOOD FLOW FOLLOWING FEMORAL ANGIOGRAPHY WITH A NEW NON-IONIC CONTRAST MEDIUM

An experimental investigation in dogs

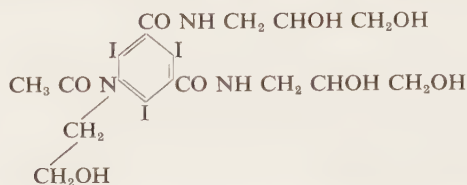
U. NYMAN and T. ALMÉN

In femoral angiography in man the ionic monomeric water-soluble contrast media in current use produce an increased blood flow in the femoral artery (DELIUS & ERIKSON 1969, BOIJSEN et coll. 1971). From animal experiments it has been concluded that this increase in blood flow is to some extent caused by the hypertonicity of the contrast medium solutions relative to plasma, producing vasodilatation in the femoral vascular bed (HILAL 1966, LINDGREN et coll. 1967, 1968 a, b).

In the research laboratories of Nyegaard & Co several non-ionic water-soluble contrast media have been synthesized. These compounds have a lower osmolality at equivalent iodine concentrations when compared with the ionic angiographic media commonly used today. One non-ionic compound, Amipaque (metrizamide), is in clinical use as contrast medium in the subarachnoid space on account of its low neurotoxicity. Amipaque also has properties advantageous for use in femoral angiography. Animal experiments (ALMÉN & TRÄGÅRDH 1973) and clinical trials (ALMÉN et coll. 1977) have demonstrated that metrizamide in femoral angiography produces less changes in the femoral blood flow and is less painful than the ionic monomeric contrast media in current use.

Partly supported by the Swedish Medical Research Council (Project No. 3483). Submitted for publication 16 December 1977.

A new contrast medium has been synthesized by Nyegaard & Co in order to find a medium with the same low toxicity as that of metrizamide but with lower viscosity and better stability when autoclaved. This compound, C29, is a benzene derivative in which three hydrogens have been replaced with iodine and the remaining three hydrogens replaced with radicals containing hydroxyl groups to achieve water-solubility:



The effects on femoral blood flow, aortic blood pressure and venous blood pressure in the hind leg of the dog caused by femoral angiography with C29 were compared with those of one ionic (Urografin) and one non-ionic contrast medium (Amipaque).

Material and Methods

Ten mongrel dogs of both sexes weighing 9 to 41 kg were anesthetized with intravenous pentobarbitone. An endotracheal tube was inserted for maintenance of free respiratory pathway. Depth of anesthesia during the experiments was characterized by regular costal and diaphragmatic respiration, presence of corneal and light reflexes and absence of eyelid reflex.

In all 10 dogs blood flow through the left femoral artery, aortic pressure and blood pressure in a vein of the left hind leg were monitored before, during and after injections of contrast medium solutions into the left femoral artery.

Injections of contrast medium solutions were made through a catheter (PE 60, Clay Adams), which was inserted in retrograde direction into a small muscle branch of the surgically exposed left femoral artery in the proximal part of the thigh. The catheter was tied in the vessel with its tip at a distance of about 2 mm from the lumen of the femoral artery.

In each dog all contrast medium solutions, which had an iodine concentration of 280 mg I/ml, were injected in random order at 2 dose levels, 0.1 ml and 0.2 ml/kg body weight. The injection time was approximately 2 s at the lower dose level and 4 s at the higher dose level.

The following contrast medium solutions were injected:

Urografin (meglumine/sodium diatrizoate, Schering) diluted with water to 280 mg I/ml; osmolality 1.5 osm; viscosity 7.2 cP at 20°C.

Amipaque (metrizamide, Nyegaard); osmolality 0.5 osm; viscosity 9.6 cP at 20°C.

C29 (an experimental non-ionic contrast medium, Nyegaard); osmolality 0.5 osm; viscosity 8 cP at 20°C.

In addition injections of physiologic saline were made in 9 of the 10 dogs at the same dose levels.

Femoral blood flow was recorded by a square wave electromagnetic flow meter (372 M, Nycotron) which was used as a mean value flow meter with a time constant of approximately 2.5 s. In addition the flow meter was equipped with an integrator summing up the total volume of fluid passing the transducer independent of rate or type of flow. A suitable flow transducer was adapted around the left femoral artery 2 to 4 cm proximal to the injection site. Zero flow was controlled by clamping the vessel distal to the flow transducer with no branching vessels between these 2 points.

In all experiments continuous simultaneous recording from the mean value flow meter and registrations of integrated fluid volumes were made during one min before and 3 min after each injection of the test solution. The maximum increase in mean blood flow in the femoral artery after injection was expressed as percentage of the highest mean blood flow recorded during a one-min period before the injection. From registrations of the integrated fluid volumes, the average blood flow during one min before and 3 min after the injection was calculated. The average increase in blood flow was expressed as percentage of the blood flow before the injection.

Aortic blood pressure was measured through a catheter (PE 90, Clay Adams), which was inserted into a small branch of the right femoral artery and manipulated into the abdominal aorta. The maximum decrease in systolic pressure after injection of a test solution was expressed as percentage of the lowest systolic pressure recorded during a one-min period before the injection.

Venous blood pressure was measured through a catheter (PE 90, Clay Adams), which was introduced into a superficial subcutaneous vein and advanced about 10 cm in proximal direction until its tip was about 5 cm distal to the left stifle joint. The maximum increase in venous pressure was expressed as percentage of the maximum value recorded during a one-min period before the injection.

The pressure catheters were connected to a pressure transducer (EMT 34, Siemens-Eléma) and recordings of blood pressure and mean blood flow were made on a Mingograf (Siemens-Eléma).

Femoral angiography was performed in 5 of the dogs at the lower dose level and in 3 of the dogs at the higher dose level.

Wilcoxon's rank test for pair differences was used for statistical analysis of the results and a difference with a p -value ≤ 0.05 was considered significant.

Results

Blood flow through femoral artery

Recording by the mean value flow meter. During and immediately after the injection of the test solution, a short decrease in blood flow was recorded followed by an increase with a maximum about half a minute after the start of the injection. At the dose

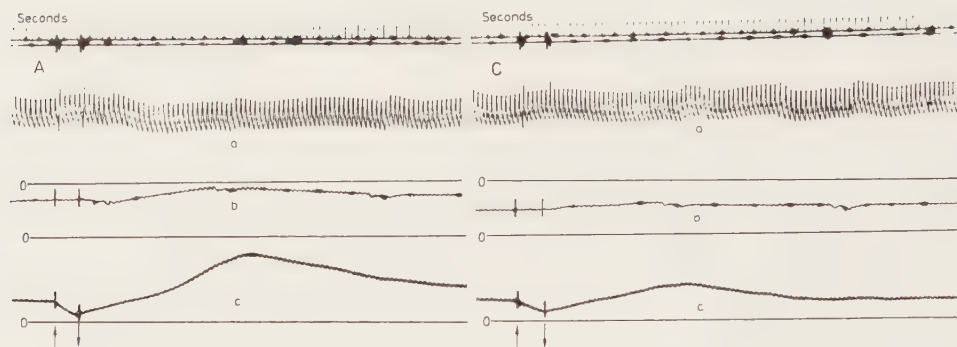


Fig. 1. Recordings of a) aortic blood pressure, b) venous blood pressure in the left hind leg and c) mean blood flow through the left femoral artery before, during and after injection (0.2 ml/kg body weight) of Urografin (A) and C29 (C) into the left femoral artery. Time of injection ($\uparrow\downarrow$).

0.1 ml/kg body weight injections of the different test solutions caused the following maximum increase in mean blood flow (median values): Urografin 213 per cent, Amipaque 53 per cent, C29 48 per cent and saline 9 per cent. At the dose 0.2 ml/kg body weight the maximum increase in mean blood flow was: Urografin 325 per cent, Amipaque 160 per cent, C29 85 per cent and saline 9 per cent.

At both dose levels Urografin caused a significantly ($p < 0.01$) higher maximum increase in mean blood flow than the other media. No significant difference between Amipaque and C29 was recorded (Figs 1, 2 a).

Registration of integrated blood volume. The average increase in blood flow rate during 3 min caused by the injection of the different test solutions at a dose of 0.1 ml/kg body weight (median values) was: Urografin 64 per cent, Amipaque 15 per cent, C29 6 per cent and saline 3 per cent. At a dose of 0.2 ml/kg body weight the corresponding figures were: Urografin 74 per cent, Amipaque 24 per cent, C29 20 per cent and saline 1 per cent. At both dose levels Urografin produced a significantly ($p \leq 0.01$) higher average increase in blood flow rate during a 3-min period than the other media, whereas there was no significant difference between Amipaque and C29 (Fig. 2 b).

The blood flow returned to pre-injection value within 3 min following injection of Amipaque and C29; after injection of Urografin the blood flow was still increased at that time but returned to pre-injection level before the next injection.

Aortic pressure

Following the injection of contrast medium a slight decrease in systolic and diastolic aortic pressure often occurred, reaching the lowest values within 30 s after the injection and then returning to pre-injection level. The maximum changes in systolic pressure following injection was as follows at a dose of 0.1 ml/kg body weight of the different test solutions (median values):

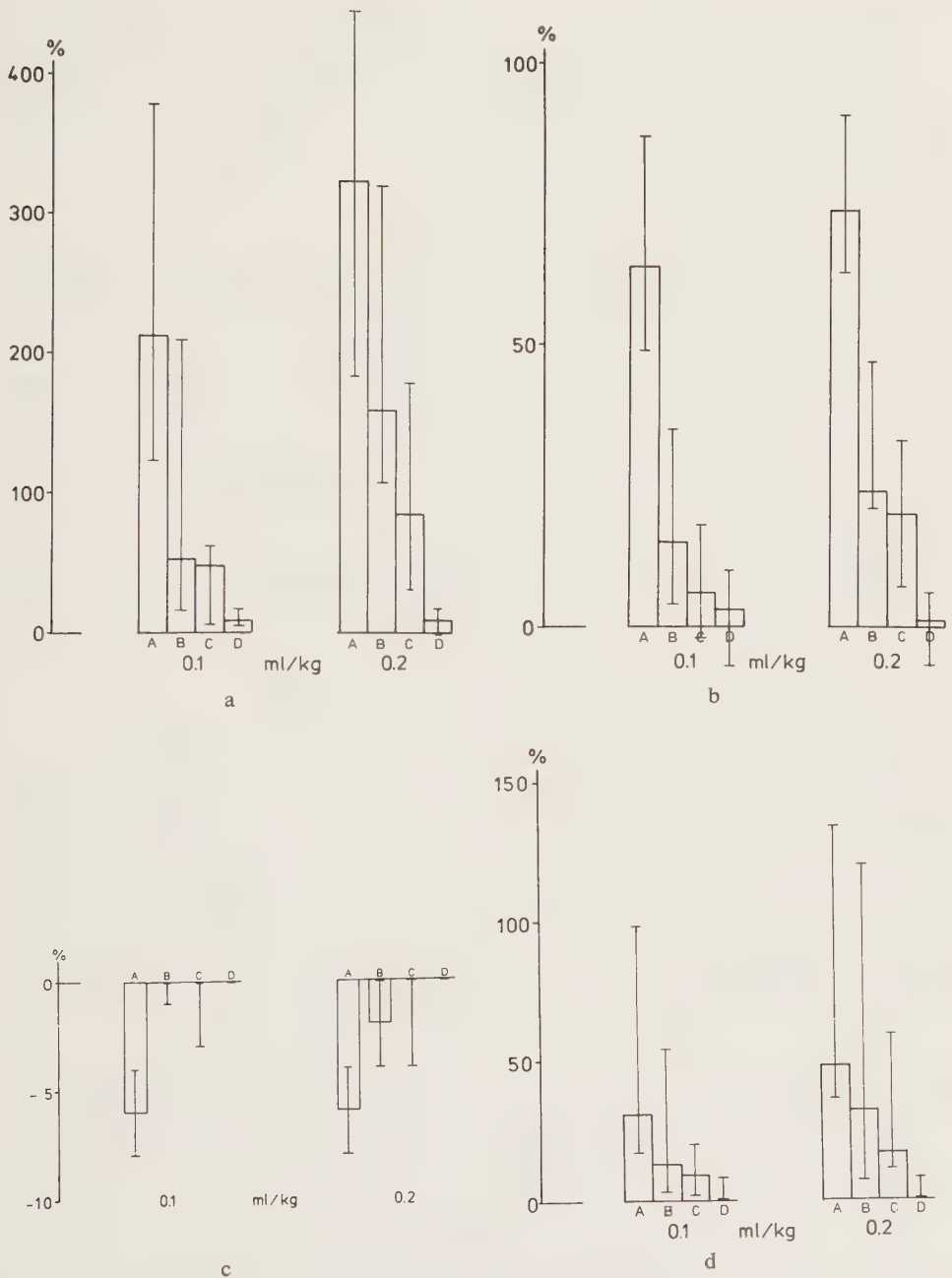


Fig. 2. Changes in blood flow in the left femoral artery, a) maximum increase, b) average increase during a 3-min period. c) Aortic blood pressure, d) venous blood pressure in the left hind leg after injection of the test solutions in the left femoral artery at 2 dose levels, 0.1 and 0.2 ml/kg body weight. Median values, first and third quartiles outlined. A = Urografin, B = Amipaque, C = C29, D = physiologic saline.

Urografin - 6 per cent, Amipaque 0 per cent, C29 0 per cent and saline 0 per cent. At a dose of 0.2 ml/kg body weight the corresponding figures were: Urografin - 6 per cent, Amipaque - 2 per cent, C29 0 per cent and saline 0 per cent. The aortic pressure changes induced by Urografin at both dose levels were significantly ($p \leq 0.02$) greater than those induced by the other media. No significant difference between Amipaque and C29 was recorded (Figs 1, 2 c).

Venous pressure

Following contrast medium injection the peripheral venous pressure of the hind leg increased, reaching a maximum at about the same time as the flow in the femoral artery. The various test solutions produced the following changes in venous pressure at a dose of 0.1 ml/kg body weight (median values): Urografin 31 per cent, Amipaque 13 per cent, C29 9 per cent and saline 0 per cent. At a dose of 0.2 ml/kg body weight the corresponding figures were: Urografin 48 per cent, Amipaque 32 per cent, C29 17 per cent and saline 0 per cent. At the lower dose level Urografin produced a significantly ($p \leq 0.01$) higher increase in venous pressure than the other media. At both dose levels no significant difference between Amipaque and C29 was recorded. At the higher dose level Urografin produced a significantly ($p \leq 0.01$) higher increase in venous pressure than C29, while no significant difference between Urografin and Amipaque occurred at this dose level (Figs 1, 2 d).

Effect of physiologic saline

Saline induced a slight increase in femoral blood flow with a maximum about 20 s after the injection. Venous blood pressure increased only in 3 of the 9 dogs while aortic pressure was not affected in any of the dogs. At both dose levels the changes of the different parameters induced by Urografin were significantly ($p \leq 0.01$) greater than the changes induced by saline. The increase in blood flow and venous pressure at the higher dose level was significantly ($p \leq 0.01$) higher for Amipaque and C29 when compared with saline. No significant difference at the lower dose level was recorded. Amipaque, C29 and saline had about the same effect on the aortic blood pressure.

Femoral angiography

The contrast medium concentration in the arteries and veins, as evaluated from the films, seemed to be the same following injection of the various contrast media and no difference between the media was recorded regarding the time of appearance in the femoral vein.

Discussion

At both dose levels investigated, Urografin produced significantly greater increase in blood flow than Amipaque or C29, irrespective of the mode of evaluation (maximum change in mean blood flow with a time constant of 2.5 s, or average change in blood flow during a 3-min period). Concerning the effect on femoral blood flow, no signi-

ficant difference between Amipaque and C29 was recorded at any dose level; moreover, these 2 non-ionic contrast media did not differ significantly from the effect of saline on blood flow at the lower dose level.

The increase in femoral blood flow was generally accompanied by a decrease in aortic pressure and an increase in venous blood pressure, i.e. a decrease of the pressure gradient over the peripheral vessels. Urografin, which caused the highest increase in blood flow, also produced the greatest changes in aortic and venous pressure. The decrease in pressure gradient cannot be due to changed physical properties of the blood since contrast media induce an increased plasma viscosity and decreased deformability of red blood cells (ASPELIN 1976). Both these factors should increase the pressure gradient over the peripheral vessels at a constant flow rate. Hence, the increase in blood flow and decrease in pressure gradient must be caused by a decrease of the resistance that is exerted by the peripheral vessels. The present results thus support the concept that contrast media in femoral angiography increase femoral blood flow by dilating peripheral branches of the femoral artery.

Urografin has an osmolality about 3 times higher than that of Amipaque and C29; it also produced a greater increase in femoral blood flow than the 2 latter media. These findings are in agreement with those of HILAL and LINDGREN *et coll.* (1967, 1968 a, b), which indicate that the vasodilatory effect of water-soluble contrast media is related to their hypertonicity relative to plasma. However, it must be remembered that it has been demonstrated both for ionic and non-ionic media that the osmolality of the contrast medium solution is not the only factor determining its vasodilatory effect. LINDGREN & TÖRNELL (1958) and LINDGREN *et coll.* (1967, 1968 a) have demonstrated that the previously used contrast medium, acetrizoate, was a stronger vasodilator than the media in common use today, diatrizoate, iothalamate and metrizoate, in spite of a similar osmolality in iodine-equivalent concentration. ALMÉN & TRÄGÅRDH reported that the vasodilatory effect of the non-ionic metrizamide was less than that of 'Compound-17', which was another non-ionic medium with an osmolality similar to that of metrizamide. Therefore, it must be concluded that the vasodilatory effect of a contrast medium is caused not only by the osmolality of the solution but also by the chemotoxicity of the molecules *per se* and that this is valid for both ionic and non-ionic contrast media.

In the selection of contrast medium for femoral angiography, the medium which produces least changes in femoral blood flow, least risk of fall in aortic blood pressure and least pain should be preferred. Non-ionic contrast media should therefore be preferred to ionic monomeric media. The 2 non-ionic media, Amipaque and C29, produce the same hemodynamic changes during femoral angiography but C29 has the potential advantages of a lower viscosity and a better stability on autoclaving than Amipaque.

SUMMARY

At femoral angiography in dogs the effects of a new non-ionic contrast medium (C29) were compared with those of one non-ionic medium (metrizamide) and one ionic medium (meglu-

mine/sodium diatrizoate) in current use. In the leg subjected to angiography the pressure gradient over the peripheral vessels decreased and the femoral blood flow increased. The changes induced by the ionic medium were significantly greater than those induced by metrizamide and C29, whereas no significant difference between the two non-ionic media was recorded.

ZUSAMMENFASSUNG

Bei femoraler Angiographie des Hundes wurden die Effekte eines neuen nicht-ionisierten Kontrastmittels (C29) mit denen von einem nicht-ionisierten Mittels (Metrizamid) und einem ionisierten Mittels (Meglumin/Natrium Diatrizoat) in allgemeinen Gebrauch verglichen. In der mit Angiographie untersuchten Extremität fiel der Druckgradient in den peripheren Gefässen und die femorale Durchblutung stieg. Die Veränderungen, die durch das ionisierte Mittel hervorgerufen wurden, waren signifikant grösser als die durch Metrizamid und C29 hervorgerufenen, während keine signifikanten Unterschiede zwischen den beiden nicht-ionisierten Mitteln zu registrieren waren.

RÉSUMÉ

Les auteurs ont comparé au cours de l'angiographie fémorale sur des chiens les effets d'un nouveau moyen de contraste non ionique (C29) avec ceux d'un moyen de contraste non ionique (métrizamide) et un moyen de contraste ionique (diatrizoate de méglumine-sodium) d'usage courant. Dans la patte angiographiée le gradient de pression sur les vaisseaux périphériques a diminué et le débit sanguin fémoral a augmenté. Les modifications produites par le moyen de contraste ionique sont nettement plus importantes que celles produites par le métrizamide et le C29 alors qu'il n'y a pas de différence notable entre les 2 moyens de contraste non ionique.

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EFFECT OF pH, BUFFER AND OSMOLALITY OF DIFFERENT CONTRAST MEDIA ON AORTIC BLOOD PRESSURE IN THE RABBIT

U. NYMAN, T. ALMÉN and M. LANDTMAN

Injections of modern ionic monomeric contrast media (iothalamate, metrizoate and diatrizoate, Fig. 1a, b, c) and other hypertonic solutions into the aorta and peripheral arteries are often painful and produce a decrease in peripheral vascular resistance (LINDGREN & TÖRNELL 1958, MARSHALL & SHEPHERD 1959, READ et coll. 1960, HILAL 1966, LINDGREN et coll. 1967, 1968, EISEN & MUNKNER 1968, DELIUS & ERIKSON 1969, OVERBECK & GREGA 1970, CHAHINE & RAIZNER 1976). Both experimental and clinical investigations indicate that such injections of metrizamide, a non-ionic monomeric contrast medium (Fig. 1d) cause less pain and less hemodynamic changes than currently used ionic monomeric media (ALMÉN 1973 a, b, ALMÉN & TRÄGÄRDH 1973, MEVES et coll. 1978).

The ionic monomeric contrast media have a ratio of 3/2 (=1.5) for the number of iodine atoms/number of particles in an ideal solution compared with a ratio of 3/1 (=3.0) for metrizamide (Fig. 2). At equal iodine concentrations metrizamide has a lower osmolality than an ionic monomeric medium. Metrizamide has the drawback of not tolerating autoclaving. It is sterilized by filtration and then freeze-dried, and supplied as a powder which has to be dissolved in water before use. Sterile filtration and freeze-drying is more expensive than autoclaving.

C29 and ioxaglate are two new contrast media with a ratio of 3.0 (Fig. 1e, f). C29 is a non-ionic monomer and ioxaglate a monoacidic dimer. They

tolerate autoclaving, but the stability of a contrast medium solution during autoclaving may vary with its pH and buffer used. The effect on aortic blood pressure following intra-aortic injections of different contrast media with variation of pH, buffer and ratio of the solutions has been investigated and was compared with that of hypertonic solution of sodium chloride.

Material and Methods

Forty male rabbits weighing 3.0 to 4.2 kg were used. Following intravenous anesthesia with pentobarbitone, the animals were placed supine and fixed with their legs slightly extended. A polyethylene catheter (PE 90, Clay Adams) was introduced via a femoral artery and placed with its tip in the abdominal aorta at the level of the third lumbar vertebra. The catheter was used both for injection of the solutions and blood pressure measurements. It was connected through a 3-way stopcock to a pressure transducer (EMT 34, Siemens-Elema). The blood pressure in the abdominal aorta was continuously recorded on a Mingograf (Siemens-Elema) for one min before and 3 min after the injections. The connection between the catheter and transducer was temporarily switched off for 3 to 5 s while injections of the solutions were

Submitted for publication 19 November 1979.

performed. During this period the blood pressure could not be recorded.

Four separate experimental series were carried out. In the first 3 (groups 1–3) the effect on aortic blood pressure from variation of pH and buffer in solutions of metrizamide and C29 was analysed and compared with the effect of media with a ratio of 1.5. In the fourth experiment (group 4) the effect of all media with a ratio of 3.0 and one with a ratio of 1.5 was analysed and compared with equiosmolal solutions of sodium chloride (Table).

In each group all solutions were injected only once in each animal. The injections were made manually and in random order in a dose of 2 ml at room temperature, except for group 4 where the solutions were preheated to 310°K (37°C). The time of injection was about 1 second. A time interval of at least 10 min elapsed between each injection. The contrast media had a concentration of 0.74 mol/l except for ioxaglate which had a concentration of 0.37 mol/l. This gives an iodine concentration for all media of 280 mg/ml. At these concentrations the media with a ratio of 1.5 (iothalamate, metrizoate and diatrizoate) and sodium chloride 0.75 mol/l have an osmolality of approximately 1.5 mol/kg while the media with a ratio of 3.0 (metrizamide, ioxaglate and C29) and sodium chloride 0.25 mol/l have an osmolality of approximately 0.5 mol/kg. The statistical analysis was made according to the Wilcoxon's test for paired differences and a p-value of 0.05 or less was considered significant.

Results

The aortic blood pressure varied slightly with respiration but was otherwise stable throughout the experiments and changed only following injection of the test solutions (Fig. 3). The results are summarized in the Table.

Effect of contrast media (groups 1 to 4). Following injection of the contrast medium solutions both systolic and diastolic blood pressure decreased with the exception for 9 of 88 injections of the ratio 3.0 media at pH 7.3 to 7.4, where no changes occurred. The decrease in blood pressure reached a minimum approximately 10 s after the injections and returned to preinjection values within one min. Metrizamide and C29 independent of pH and buffer, and ioxaglate caused significantly less decrease in aortic blood pressure than the ratio 1.5 media with which they were compared. No significant difference existed

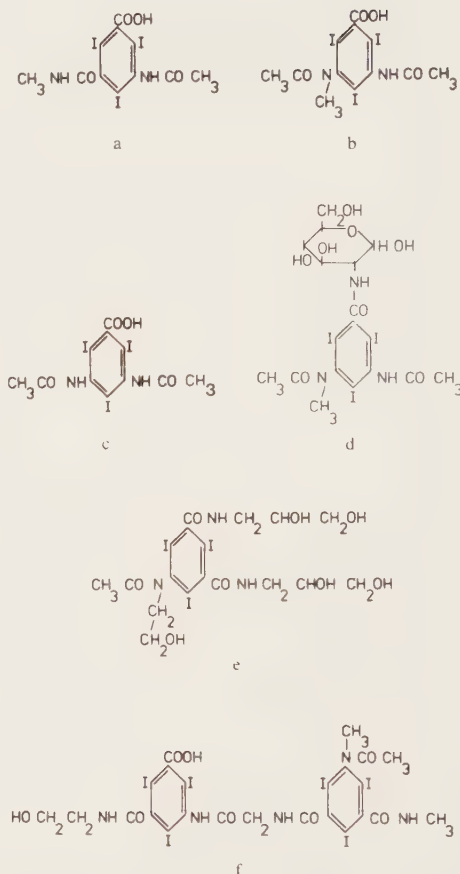


Fig. 1. a) Iothalamic acid (Conray Meglumin = meglumine iothalamate). b) Metrizoic acid (Isopaque Cerebral = meglumine metrizoate/calcium metrizoate-52.3/1 w/w). c) Diatrizoic acid (Urografin 60% = meglumine diatrizoate/sodium diatrizoate—6.6/1 w/w—diluted with water to 280 mg l/ml). d) Metrizamide (Amipaque). e) C29. f) Ioxaglate (meglumine ioxaglate/sodium ioxaglate-2/1 w/w).

between metrizamide, C29 and ioxaglate at pH 7.4 (group 4). In group 2 no significant difference was found between iothalamate and diatrizoate.

Effect of non-ionic contrast media with different pH and buffer (groups 1 to 3). Increasing the acidity of the non-ionic contrast media increased the changes in aortic blood pressure. Metrizamide at pH 7.4 caused significantly less fall in aortic blood pressure than at pH 5.0 (group 1). The same significant difference was noted between C29 at pH 7.3 and 5.0 (group 2). When metrizamide and C29 were dissolved in different buffering systems (phosphate,

	Chemical structure	Ratio
a.	$\text{Na}^+ \quad \text{I}^-$	$\frac{1}{2} = 0.5$
b.	$\text{Na}^+ \quad \text{I}-\text{C}_5\text{H}_4\text{N}-\text{COO}^-$	$\frac{2}{2} = 1$
c.	$\text{Na}^+ \quad \text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{COO}^-$	$\frac{3}{2} = 1.5$ Ionic monomeric
d.	$\text{Na}^+ \quad \text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{COO}^- \quad \text{Na}^+ \quad \text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{COO}^-$	$\frac{6}{3} = 2$ Diacidic dimeric
e.	$\text{Na}^+ \quad \text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{R} \quad \text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{COO}^-$	$\frac{6}{2} = 3$ Monoacidic dimeric
f.	$\text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{ROH}$	$\frac{3}{1} = 3$ Non-ionic monomeric
g.	$\text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{ROH} \quad \text{I}-\text{C}_6\text{H}_3\text{I}_2-\text{ROH}$	$\frac{6}{1} = 6$ Non-ionic dimeric

Fig. 2. Chemical structure and ratio of clinical or experimental contrast media. The letter R indicates not specified chemical structure. Media in a-e) are ionic solutions while f) and g) are

non-ionic solutions. The development of contrast media from a to g) has meant an increase of the ratio with a factor of 12 with a subsequent decrease in osmolality at equal iodine concentrations.

TRIS and bicarbonate) at pH 7.3 to 7.4, no significant difference in the response (groups 1 and 3) occurred. Unbuffered solutions of metrizamide (hydrochloric acid) at pH 5.0 produced the same decrease in blood pressure as buffered solutions of metrizamide (phosphate buffer) at the same pH (group 1).

Effect of unbuffered hypertonic solutions of sodium chloride (group 4). Sodium chloride 0.75 mol/l produced the same decrease in aortic blood pressure as diatrizoate, but the duration of the decrease was significantly shorter (median 16 s) than after diatrizoate (median 25 s). Sodium chloride 0.25 mol/l caused no significant alteration in aortic blood pressure.

Discussion

According to previous comprehensive experimental and clinical investigations, decrease in arterial blood pressure following injections of contrast

media and hypertonic solutions of sodium chloride into the aorta and peripheral arteries is due to a decrease in peripheral vascular resistance (READ et coll., OVERBECK et coll. 1961, HILAL, EFSEN & MUNKNER, DELIUS & ERIKSON, CHAHINE & RAIZNER. This decrease has been attributed to a local effect on the peripheral vessels of the injected solutions causing vasodilatation.

Hypertonicity. The vasodilatory properties of ionic monomeric contrast media in current clinical use have to a large extent been related to their hypertonicity relative to plasma. The effect is similar to that of other solutions in equiosmolal concentrations such as sodium chloride, glucose, mannitol and urea (HILAL, KLOSTER et coll. 1967, LINDGREN et coll. 1967). An increase in the ratio of contrast media from 1.5 (ionic monomeric media) to 2.0 (diacidic dimeric media) and further to 3.0 (non-ionic monomeric and monoacidic dimeric media)

Table

Decrease in aortic systolic blood pressure following intra-aortic injection. The figures represent the maximum decrease in systolic pressure after the injection expressed in percentage of the lowest systolic pressure during one min before the injection. Median value and range are given

	pH	Decrease
Group 1 (n = 12)		
Meglumine/calcium metrizoate (Isopaque Cerebral)	7.2	18.3 (11.3–24.4)
Metrizamide dissolved in diluted hydrochloric acid	5.0	10.3 (6.1–23.5)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	5.0	11.3 (5.1–25.7)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	5.5	7.3 (2.9–12.0)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	6.2	6.4 (2.8–10.5)
Metrizamide dissolved in sodium phosphate buffer 0.01 mol/l	7.4	5.1 (0.0–13.6)
Metrizamide dissolved in sodium bicarbonate buffer 0.0006 mol/l (Ampaque)	7.4	5.8 (0.0–13.1)
Group 2 (n = 10)		
Meglumine iothalamate (Conray Meglumin)	7.3	19.5 (11.4–29.4)
Meglumine/sodium diatrizoate (Urografin)	7.0	18.0 (13.5–31.4)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	5.0	10.5 (1.3–20.0)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	6.0	6.8 (2.7–18.3)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	7.3	5.0 (0.0–10.5)
Group 3 (n = 8)		
Meglumine/calcium metrizoate (Isopaque Cerebral)	7.3	20.1 (13.9–30.0)
C29 dissolved in sodium phosphate buffer 0.01 mol/l	7.3	7.6 (3.0–10.5)
C29 dissolved in TRIS-buffer ((CH ₂ OH) ₃ CNH ₂) 0.01 mol/l	7.4	5.0 (3.1–9.8)
Metrizamide dissolved in sodium bicarb. buffer 0.0006 mol/l (Ampaque)	7.4	6.1 (3.0–9.0)
Group 4 (n = 10)		
Meglumine/sodium diatrizoate (Urografin)	7.0	15.8 (2.3–45.1)
C29 dissolved in TRIS-buffer 0.01 mol/l	7.4	10.0 (0.0–29.5)
Meglumine/sodium ioxaglate	7.4	9.3 (0.0–28.8)
Metrizamide dissolved in sodium bicarb. buffer 0.0006 mol/l (Ampaque)	7.4	7.0 (0.0–28.2)
Sodium chloride unbuffered solution 0.75 mol/l	5.5	16.2 (4.6–50.0)
Sodium chloride unbuffered solution 0.25 mol/l	5.5	0.0 (0.0–1.1)

represents a gradual decrease in osmolality of solutions at iodine equivalent concentrations and gradually decreased effect of peripheral vascular resistance (HILAL, BJÖRK et coll. 1969, ALMÉN & TRÄGÄRDH, ALMÉN et coll. 1977, NYMAN & ALMÉN 1978). The present results are in accordance with this. Furthermore, the reproduction of an identical hemodynamic response using contrast medium solutions which differ in regard to cation content, chemical structure of the iodinated organic molecule, viscosity or other physico-chemical properties except for osmolality supports the concept that hypertonicity of the solutions is the main factor causing vasodilatation.

Sodium chloride in concentrations equiosmolal with the ratio 3.0 contrast media caused no obvious changes in aortic blood pressure while the media with a ratio of 3.0 did. In addition, the hypotensive

reaction lasted longer following injection of diatrizoate than following equiosmolal solutions of sodium chloride. This indicates that factors other than hypertonicity may contribute to vasodilatation and the relative importance of such factors may increase when the osmolality is reduced.

Chemotoxicity. LINDGREN et coll. (1968) demonstrated that acetrizoate, a previously used ratio 1.5 contrast medium, was a stronger vasodilator than the ratio 1.5 media used in the present experiments. ALMÉN & TRÄGÄRDH reported that the vasodilatory effect of the non-ionic metrizamide was less than Compound 17, which was another nonionic medium with an osmolality similar to that of metrizamide. This difference in response of equiosmolal contrast medium solutions may result from difference in chemotoxicity of the iodinated organic molecule per se.

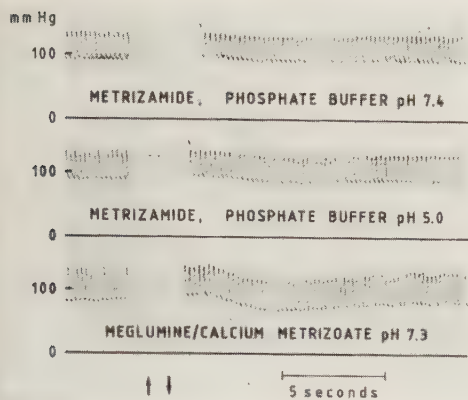


Fig. 3. Recordings of aortic blood pressure before and after injection of various contrast media into the aorta. Time of injection (↑). Start (↑), end (↓) of injection.

Viscosity. Microcirculatory investigations indicate that the high viscosity of contrast media compared with sodium chloride solutions may play some role when evaluating the difference in hemodynamic response (SØRENSEN & ASANO 1971, EKELAND & UFLACKER 1978). According to these authors intraarterial bolus injections of contrast medium solutions and sodium chloride give a short period of ischemia during their passage through the peripheral vascular bed. The duration of the ischemic or passage time was significantly longer for contrast media than for iso- and hypertonic solutions of sodium chloride, a difference that might be related to the higher viscosity of the contrast medium solutions. This would mean an increased application time for the contrast media during which they can exert their osmotic and possible chemotoxic effects. In addition the ischemic effect per se of an injected bolus may contribute to the decrease in vascular resistance. A reactive hyperemia following the ischemic period would then be more marked after injection of contrast media than after sodium chloride. Thus, the difference in hypotensive reaction noted in the present experiments between contrast media and equiosmolal solutions of sodium chloride may theoretically be explained by a chemotoxic effect of the iodinated organic molecule or by the higher viscosity of the contrast media.

The pH of the solution must also be considered when evaluating the effect on the peripheral vascular resistance. It is known that solutions both on the acid and alkaline side of the physiologic pH-

range have vasodilatory properties (ELLIOTT & JASPER 1949, KESTER et coll. 1952, DEAL & GREEN 1954, HADDY et coll. 1958). Both the present and previous results (ALMÉN 1973a) indicate that progressive alteration of the pH below 7.4 of non-ionic contrast media will increase the fall in aortic blood pressure.

According to KESTER et coll. injections of buffered acid and alkaline solutions of sodium chloride produce a decrease in peripheral vascular resistance while variation of pH of unbuffered solutions of sodium chloride do not. The difference in hypotensive effect between injections of buffered solutions of metrizamide and C29 at pH 5.0 compared with injection of the same solutions at pH 7.3 to 7.4 was therefore expected. However, metrizamide adjusted to pH 5.0 by adding hydrochloric acid, an unbuffered solution, produced the same decrease in blood pressure as a buffered solution of metrizamide at the same pH. While KESTER et coll. injected 1 ml of sodium chloride during 10 s into the femoral artery in dogs, 2 ml during 1 s was injected into the aorta in rabbits in the present experiments. These differences in methods cannot explain the hypotensive effect of unbuffered solutions of metrizamide at pH 5.0, since injections of unbuffered equiosmolal solutions of sodium chloride at pH 5.5 did not produce any fall in aortic blood pressure. One explanation may be that the ability of blood to buffer unbuffered acidic solutions of contrast media may be counteracted by their high viscosity, which delays the mixing of blood and contrast media. The unbuffered contrast media may thus still possess their acidic properties when reaching the peripheral vascular bed.

Injections of metrizamide and C29 at pH 7.3 to 7.4 with the use of phosphate, TRIS and bicarbonate as different buffering systems did not cause any difference in hypotensive reaction.

Conclusions

Contrast medium solutions for peripheral angiography should have an osmolality and a pH close to that of human plasma in order to minimize the risk of fall in arterial blood pressure. The choice of buffer (phosphate, TRIS and bicarbonate), in order to give the solutions a proper pH, seems to be of minor importance.

SUMMARY

Intra-aortic injections in rabbits of contrast media with a lower osmolality (metrizamide, C29 and ioxaglate) caused significantly less decrease in aortic blood pressure than injections of contrast media with a higher osmolality (diatrizoate, metrizoate and iothalamate) at iodine equivalent concentrations. Increasing the acidity of metrizamide and C29 from pH 7.4 to 5.0 increased the blood pressure fall. Variation of the buffer (phosphate, TRIS and bicarbonate) in metrizamide and C29 solutions at physiologic pH did not cause any difference in response.

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FROM THE DEPARTMENTS OF EXPERIMENTAL RESEARCH AND DIAGNOSTIC RADIOLOGY, MALMÖ ALLMÄNNA SJUKHUS, S-21401 MALMÖ, SWEDEN.

EFFECT OF CONTRAST MEDIA ON FEMORAL BLOOD FLOW

Comparison between non-ionic and ionic monomeric and monoacidic dimeric contrast media in the dog

ULF NYMAN, TORSTEN ALMÉN and MAGNUS LANDTMAN

Both animal experiments (LINDGREN & TÖRNELL 1958, SAKO 1963, HILAL 1966, COEL & LASSER 1971, CHAHINE & RAIZNER 1976, NYMAN & ALMÉN 1978) and clinical reports (AMUNDSEN *et coll.* 1956, EFSSEN & MUNKNER 1968, DELIUS & ERIKSON 1969, BOIJSEN *et coll.* 1971) have shown that injection of angiographic contrast media into the aorta and femoral arteries produce a transient increase in blood flow rate and decrease in arterial blood pressure. This is due to a decrease in peripheral vascular resistance, which has been ascribed to vasodilatation. Furthermore, peripheral angiography performed with currently used ionic monomeric contrast media (diatrizoate, iothalamate and metrizoate) is a painful examination (FRIEDENBERG 1964, AMUNDSEN 1965, FOG 1967).

Metrizamide, a non-ionic monomer, and ioxaglate, a monoacidic dimer, have a lower osmolality than the ionic monomers in equivalent iodine concentrations. Several reports indicate that these media cause considerably less pain and hemodynamic changes when injected into the aorta and femoral arteries (ALMÉN & TRÄGÅRDH 1973, ALMÉN *et coll.* 1977, AMIEL *et coll.* 1978, MEVES *et coll.* 1978, NYMAN & ALMÉN, HOLM & PRAESTHOLM 1979, TILLMANN *et coll.* 1979).

The vasodilatory properties of contrast media with different osmolality reflected as changes in local blood flow following their injection into the femoral artery of the dog has been investigated. The intention was to explore the role of osmolality of the

media in producing vasodilatation and to analyse the new non-ionic medium, iohexol.

Material and Methods

Twenty mongrel dogs of both sexes weighing 13 to 37 kg were used. Anaesthesia was initiated with an intravenous injection of pentobarbitone sodium (Nembutal, Abbott), 25 mg/kg body weight. Additional doses, 2.5 to 5.0 mg/kg, were given during the experiment when necessary. An endotracheal tube was inserted to maintain free respiratory pathway.

The femoral artery was exposed via an incision in the proximal part of the thigh. All muscular branches were ligated and cut, except one which was used for retrograde insertion of a polyethylene catheter (PE 60, Clay Adams). The tip of the catheter was positioned about 2 mm from the lumen of the femoral artery and fixed with a ligature around the muscular branch. The test solutions were injected manually through this catheter.

Proximal to the site of injection a flow transducer was placed around the femoral artery and connected to a square wave electromagnetic flow meter (372-M, Nycotron). Isotonic sodium chloride was instilled into the explored region covering the femoral artery and transducer.

Mean blood flow rate was continuously recorded on a Mingograf (Siemens-Elema) one minute before, during and three min after the injections. Simulta-

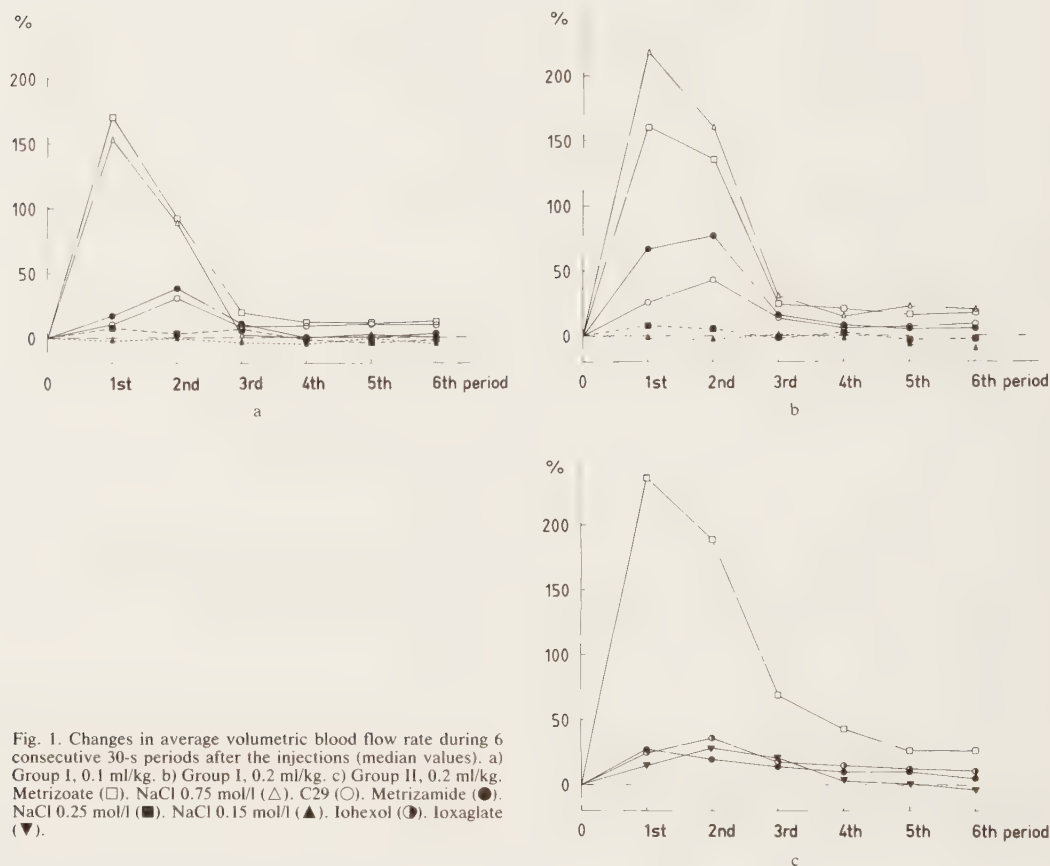


Fig. 1. Changes in average volumetric blood flow rate during 6 consecutive 30-s periods after the injections (median values). a) Group I, 0.1 ml/kg. b) Group I, 0.2 ml/kg. c) Group II, 0.2 ml/kg. Metrizoate (□). NaCl 0.75 mol/l (△). C29 (○). Metrizamide (●). NaCl 0.25 mol/l (■). NaCl 0.15 mol/l (▲). Iohexol (◐). Ioxaglate (▼).

neously the blood volumes passing the transducer during consecutive 30-second periods were registered by an integrator. The maximum increase in mean blood flow rate after each injection was expressed in percentage of the highest mean blood flow rate before the injection. From registrations of the integrated blood volumes, changes in average volumetric flow rate during 6 consecutive 30-s periods and a 3-min period after the start of the injection were expressed in percentage of the average volumetric flow rate before the injection.

Zero flow reference was controlled before the first injection by clamping the femoral artery distal to the flow transducer. Additional controls were performed after every third and after the last injection in each experiment. Any drift in zero flow was adjusted immediately.

Test solutions

Group I ($n=10$)

Meglumine/calcium metrizoate (w/w 59/1, Isopaque Cerebral	pH 7.3
Metrizamide dissolved in sodium bicarbonate buffer, substance concentration 0.6 mmol/l (Amipaque)	pH 7.4
C29 dissolved in TRIS buffer, substance concentration 0.01 mol/l (an experimental non-ionic monomer)	pH 7.4
Sodium chloride, substance concentration 0.15 mol/l	pH 5.5
Sodium chloride, substance concentration 0.25 mol/l	pH 5.5
Sodium chloride, substance concentration 0.75 mol/l	pH 5.5

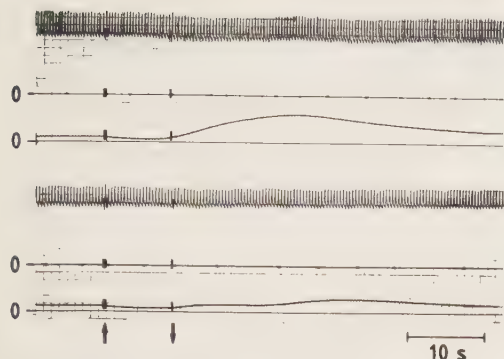


Fig. 2. Recordings of aortic blood pressure and mean femoral blood flow rate from one experiment before, during and after injection (0.2 ml/kg body weight) of metrizoate (top) and iohexol (bottom).

Group II (n=10)

Meglumine/calcium metrizoate (w/w 59/1, Isopaque Cerebral)	pH 7.3
Metrizamide dissolved in sodium bicarbonate buffer, substance concentration 0.6 mmol/l (Amipaque)	pH 7.4
Iohexol dissolved in TRIS buffer, substance concentration 0.01 mol/l	pH 7.4
Meglumine/sodium ioxaglate (w/w 2/1, Hexabrix)	pH 7.4

In addition in group II the aortic blood pressure was continuously recorded through a polyethylene catheter (PE 90, Clay Adams) inserted via a muscular branch of the opposite femoral artery. The catheter was connected to a pressure transducer (EMT-34, Siemens-Elema) and the pressure was recorded on a Mingograf.

The chemical structure of the different contrast media has been given by HAAVALDSEN (1980). All contrast medium solutions had an iodine concentration of 280 mg/ml corresponding to a substance concentration of 0.37 mol/l for ioxaglate and 0.74 mol/l for the other compounds. At these concentrations metrizoate and sodium chloride, substance concentration 0.75 mol/l, have an osmolality of approximately 1.5 mol/kg, while the non-ionic monomers, ioxaglate and sodium chloride, substance concentration 0.25 mol/l, have an osmolality of about 0.5 mol/kg. Sodium chloride, substance concentration 0.15 mol/l is isotonic with plasma.

The solutions were preheated to 310°K (37°C) and

injected in random order in a dose of 0.1 and 0.2 ml/kg body weight in group I and 0.2 ml/kg body weight in group II. The rate of injection was approximately 1 ml/s. An interval of 10 min passed between the individual injections.

Wilcoxon's rank test for paired observations was used for statistical analysis and a difference with a p-value of 0.05 or less was considered significant.

Results

The blood flow before the injections varied during the course of the experiments. No significant difference existed between pre-injection flow values of the various solutions.

The proximal position of the flow transducer relative to the site of injection consequently resulted in the recording of a decrease in blood flow rate during the injections. Following injection of the contrast media and sodium chloride, substance concentration 0.75 mol/l, the rate of blood flow increased and reached a peak half a minute after the start of the injections. Blood flow had generally returned to pre-injection values within 3 min after the injections.

In the individual experiments sodium chloride, substance concentration 0.15 and 0.25 mol/l, had no effect at all or produced an increase in blood flow rate of short duration with a peak about 10 s after the start of the injections.

The results are summarized in Tables 1 and 2 and Fig. 1. An experimental situation is illustrated in Fig. 2.

Group I. Metrizamide and C29 caused significantly less increase in blood flow rate than metrizoate and sodium chloride, substance concentration 0.75 mol/l. No significant difference was found between metrizamide and C29 or between metrizoate and sodium chloride, substance concentration 0.75 mol/l. These results were valid for both maximum increase in mean blood flow rate and increase in average volumetric flow rate during 3 min.

The changes in blood flow (mean and volumetric flow rate) induced by sodium chloride, substance concentration 0.15 and 0.25 mol/l, were significantly less compared with the other solutions; no difference was found between these 2 solutions of sodium chloride.

Group II. Regardless of the mode of evaluation no significant difference was recorded in blood flow after injection of metrizamide, iohexol and ioxa-

Table 1

Femoral blood flow following injection of metrizoate, metrizamide, C29 and sodium chloride into the canine femoral artery in group I. A) Maximum increase in mean blood flow rate. B) Changes in average volumetric flow rate during a 3-min period. The figures represent median values and range given as percentage

Dose		Metrizoate	Metrizamide	C29	Sodium chloride, substance concentration		
					0.15 mol/l	0.25 mol/l	0.75 mol/l
0.1 ml/kg	A	211 (67/500)	65 (13/257)	38 (0/90)	0 (0/25)	11 (0/33)	259 (108/583)
	B	47 (18/114)	18 (-4/55)	11 (6/36)	-2 (-22/11)	1 (-6/28)	46 (15/106)
0.2 ml/kg	A	337 (109/471)	126 (25/483)	83 (10/340)	12 (0/80)	23 (0/67)	311 (200/780)
	B	70 (33/123)	31 (2/98)	24 (-5/60)	-3 (-15/17)	2 (-4/12)	81 (35/167)

Table 2

Femoral blood flow following injection of metrizoate, metrizamide, iohexol and ioxaglate into the canine femoral artery in group II. A) Maximum increase in mean blood flow rate. B) Changes in average volumetric flow rate during a 3-min period. The figures represent median values and range given as percentage

Dose		Metrizoate	Metrizamide	Iohexol	Ioxaglate
0.2 ml/kg	A	423 (200/1125)	79 (0/338)	72 (11/230)	45 (0/213)
	B	104 (42/96)	16 (1/106)	18 (-1/81)	9 (-4/52)

glate, and they all caused significantly less changes than metrizoate.

Aortic blood pressure was stable during the experiments. A slight fall in both systolic and diastolic pressure was noted simultaneously with the increase in flow rate following injection of metrizoate. No obvious changes were noted following injection of the non-ionic monomers and monoacidic dimer.

Discussion

All contrast medium solutions significantly increased femoral blood flow rate. The effect of the new non-ionic monomer, iohexol, was similar to that of metrizamide, C29 and ioxaglate, and all these media caused significantly less changes than metrizoate.

The occasionally noted increase in blood flow rate after injection of sodium chloride, substance concentration 0.15 and 0.25 mol/l, probably resulted from replacement and dilution of blood by a less viscous solution without any changes in vasomotor tone (DEAL & GREEN 1954). The acidity of the sodium chloride solutions should not have had any effect on blood flow, since they were injected as unbuffered solutions (KESTER et coll. 1952). Sodium chloride, substance concentration 0.75 mol/l, caused significantly larger and more prolonged changes than the other 2 sodium chloride solutions.

Currently used angiographic ionic monomeric contrast media (diatrizoate, iothalamate and metrizoate) are 5 to 7 times as hypertonic as plasma. In regard to the vasodilatory activity of these 3 contrast media in the femoral vascular bed no significant difference has previously been found (LIND-

GREN et coll. 1967, 1968). For contrast media of this group the high osmolality has been regarded to be the major factor behind their vasodilatory effect (HILAL 1966, KLOSTERS et coll. 1967, LINDGREN et coll. 1967). This is in agreement with the present experiments in which intra-arterial injections of metrizoate and sodium chloride in equiosmolal concentrations caused a similar increase in femoral blood flow rate.

The osmolality of aqueous solutions is dependent upon the number of particles dissolved per kilogram water. Therefore, attempts were made to reduce the number of particles in contrast medium solutions without reducing their iodine content. This resulted in the synthesis of diacidic dimeric and triacidic trimeric media, which had less effect on peripheral vascular resistance than ionic monomeric media (BJÖRK et coll. 1969, HILAL 1970). In order to achieve a further reduction of the number of particles and thereby the osmolality non-ionic monomers and monoacidic dimers were synthesized. Animal experiments indicate that these compounds have less vasodilatory properties than both ionic monomers and diacidic dimers (ALMÉN & TRÄGÄRDH, AMIEL et coll.). This is supported by the present results.

Clinical trials have shown that diacidic and monoacidic dimers and non-ionic monomers cause significantly less pain in aorto-femoral angiography than ionic monomers (BJÖRK et coll., ALMÉN et coll., HOLM & PRAESTHOLM, TILLMANN et coll.). These findings suggest that the sensation of pain parallels the degree of hemodynamic changes caused by contrast media in animal experiments.

In the present experiments solutions of non-ionic monomers and monoacidic dimers caused significantly higher increase in the rate of femoral blood flow than equiosmolal solutions of sodium chloride. HILAL (1966) reported that sodium chloride solutions had no effect upon canine femoral blood flow below a concentration corresponding to an osmolality of about 0.6 mol/kg. The results indicate that other factors than hypertonicity are responsible for the effect of the non-ionic monomers and monoacidic dimer on the peripheral vascular resistance. Such factors might instead be a chemical effect of the iodine-bearing molecule, or effects of cations and buffers in contrast medium solutions.

When discussing the toxic effect of a contrast medium it is difficult to evaluate the role of viscosity of the solutions. In aorto-femoral angiography a

bolus of contrast medium passes through the vessels. The high viscosity of a contrast medium solution tends to prolong its time of passage through the vessels compared with less viscous solutions (SØRENSEN & ASANO 1971, EKELAND & UFLACKER 1978) and thereby also its time of contact with the vessel wall. This prolonged contact time might increase the toxic effect of the factors discussed including the osmolality. However, the high viscosity will decrease the diffusion rate of the particles in the solution (EINSTEIN 1905). Decreasing the rate of the diffusion of particles through the solvent and into the vessel wall should tend to decrease the chemotoxic effects of a bolus of a contrast medium solution.

Conclusion

The high osmolality of metrizoate is the dominating factor in its vasodilatory effect in the femoral vascular bed. For contrast media with a lower osmolality, non-ionic monomers and monoacidic dimers, other factors than hypertonicity are responsible for their effect. Iohexol seems to be an appropriate contrast medium for aorto-femoral angiography with relevance to its vasodilatory action.

SUMMARY

Injections of non-ionic monomeric (metrizamide, C29 and iohexol) and monoacidic dimeric (ioxaglate) contrast media into the femoral artery of dogs caused significantly less increase in the rate of femoral blood flow than the more hypertonic ionic monomeric compound metrizoate at equivalent iodine concentrations. The effect of metrizoate was similar to that of equiosmolal solutions of sodium chloride. Sodium chloride in concentrations equiosmolal with the non-ionic monomers and monoacidic dimer caused less changes in blood flow than these contrast media, but the changes were equal to those of isotonic sodium chloride.

ACKNOWLEDGEMENTS

This investigation was supported by grants from the Medical Faculty, University of Lund and the Swedish Medical Research Council (Project No. 3483). The technical assistance of Anita Burnett and Gail Akerman is gratefully acknowledged.

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EFFECTS OF CONTRAST MEDIA ON AORTIC ENDOTHELIUM

Experiments in the rat with non-ionic and ionic monomeric and monoacidic dimeric contrast media

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Injury to the vascular endothelium caused by contrast media has been considered to be one possible mechanism in the development of toxic effects, occurring both in animal experiments and clinical situations, following angiography (LINDGREN 1961, FLODMARK & STEINWALL 1963, MARGOLIS 1970, BINNIE *et coll.* 1971, TEJLER *et coll.* 1977a, b).

Some experiments indicate that such endothelial injury may predispose to thrombus formation (BRÅNEMARK *et coll.* 1969, RITCHIE *et coll.* 1974) and this has been supported by thrombotic side-effects following phlebography in man (CRANLEY 1975, ALBRECHTSSON & OLSSON 1976, RITCHIE *et coll.* 1977).

Contrast medium induced injuries to arterial and venous endothelium have been disclosed by staining the vessel wall with silver nitrate solution (ZINNER & GOTTLÖB 1959, MERSEREAU & ROBERTSON 1961, AUSMAN *et coll.* 1964, MCCONNELL & MERSEREAU 1964). ALMÉN *et coll.* (1973) reported that the non-ionic metrizamide induced less changes in silver stained aortic endothelium than the ionic metrizoate. This difference may partly be explained by the lower osmotic pressure of metrizamide compared with that of metrizoate.

Recently some new non-ionic monomeric media (C29, 593 and iohexol, Nyegaard & Co.) and a monoacidic dimeric compound (ioxaglate, Laboratoire Guerbet) have been synthesized with approximately the same low osmolality as metrizamide. The effect of these new contrast media on the aortic

endothelium of the rat has been investigated and the results are now reported.

Material and Methods

The material consisted of 110 male Wistar rats, weighing 200 to 250 g, which were anaesthetized with ether and an intra-abdominal injection of mebumal sodium (Mebumal Veterinary). The aorta was surgically exposed and a thin polyethylene catheter was inserted in cranial direction with its tip located in the proximal part of the abdominal aorta. The tip of the catheter was fixed with a ligature around the aorta. The heart was removed and the thoracic aorta was rinsed by an injection of isotonic sodium chloride.

The aortic endothelium was exposed to 5 ml of one of the test solutions for 5 min, thereafter the vessel was rinsed with 10 ml isotonic sodium chloride. The endothelium was then stained by 5 ml silver nitrate solution (0.25 % w/v) injected during 30 seconds. The staining was terminated by injection of 10 ml glucose (5.5 %) during one min. The vessel was finally perfused with formalin (10 %) during 30 min for primary fixation. All solutions were injected manually and at room temperature. The thoracic aorta was then carefully dissected free from surrounding connective tissue, opened ventrally and removed.

The preparation was placed with the adventitial side down on a glass slide and fixed with tape at its



Fig. 1. Normal aortic endothelium stained with silver nitrate solution.



Fig. 2. Endothelial injury with subendothelial silver lines.

proximal and distal ends to prevent curling. After fixation for 24 hours in formalin (10%) the preparation was washed in distilled water for 12 hours, dehydrated in graded alcohols (80%, 95% and absolute alcohol) for 5 min, cleared with xylene during 30 seconds and mounted with Canada balsam under a cover slip.

Normal vascular endothelium treated with silver nitrate solution and examined in a light microscope appears as a network of dark brown lines outlining the individual cells (FLOREY *et coll.* 1959, GARBARSCH & CHRISTENSEN 1970), which are oriented with their long axis parallel to the vessel axis (Fig. 1). Injury to the endothelium results in silver staining of subendothelial structures, which is characterized by roughly parallel dark stripes running at right angles to the vessel axis (Fig. 2) replacing the normal endothelial appearances (SAMUELS & WEBSTER 1952).

The aorta was examined in a light microscope at a magnification of 256 $\times$. The specimens were systematically scanned with a superimposed square network placed in the ocular allowing quantitation of the areas with subendothelial silver staining. De-

pendent on the size of the individual specimen approximately 75 to 125 viewing fields, each measuring 500 $\times$ 500 μ m, were examined. The extent of endothelial injury was expressed in percentage of the total area examined. For elimination of possible mechanical injury the marginal areas of the vessels were not measured.

The effects of the new non-ionic monomers and monoacidic dimer were compared with those of metrizamide, diatrizoate, metrizoate, and iso- and hypertonic solutions of sodium chloride. C29 solutions with different pH and buffers were available, since the stability of the contrast medium solution during autoclaving had been tested with different pH and buffers. Each solution was tested in 10 rats.

Test solutions

Sodium chloride, substance concentration 0.15 mol/l	pH 5.5
Sodium chloride, substance concentration 1.05 mol/l	pH 5.5
C29 dissolved in phosphate buffer, substance concentration 0.01 mol/l	pH 6.3

C29 dissolved in phosphate buffer, substance concentration 0.01 mol/l	pH 7.4
C29 dissolved in TRIS buffer, substance concentration 0.01 mol/l	pH 7.4
Meglumine/sodium ioxaglate (w/w 2/1, Hexabrix)	pH 7.4
593 dissolved in TRIS buffer, substance concentration 0.01 mol/l	pH 7.4
Iohexol dissolved in TRIS buffer, substance concentration 0.01 mol/l	pH 7.4
Metrizamide dissolved in sodium bicarbonate buffer, substance concentration 0.6 mmol/l (Amipaque)	pH 7.4
Meglumine/sodium diatrizoate (w/w 6.6/1, Urografin 76 %)	pH 7.0
Meglumine/sodium/calcium metrizoate (w/w 6.6/1/0.1, Isopaque Coronar)	pH 7.3

The chemical structure of these contrast media has been given by HAAVALDSEN (1980).

All contrast media were used at an iodine concentration of 370 mg/ml corresponding to a substance concentration of 0.49 mol/l for ioxaglate and 0.97 mol/l for the other contrast media. The osmolality of the non-ionic monomeric media and ioxaglate was approximately 0.6 to 0.8 mol/kg, and for diatrizoate, metrizoate and sodium chloride, substance concentration 1.05 mol/l, 2.0 to 2.2 mol/kg.

Mann-Whitney's test for unpaired observations was used for statistical analysis. A difference with a p-value of 0.01 or less was regarded significant.

Results

In all specimens scattered areas with dark parallel stripes running transversely to the long axis of the vessel were found. The injured areas often had a longitudinal extension in the vessel. The extension of subendothelial silver staining in per cent of the endothelial surface examined varied with the different test solutions and the results are presented in Fig. 3.

The changes found in specimens perfused with isotonic sodium chloride were significantly less than those found after perfusion with the other solutions. Injection of diatrizoate and metrizoate caused the most extensive changes and the differences noted compared with the other solutions were statistically significant. No significant difference was found between the various C29 solutions, 593, iohexol, me-

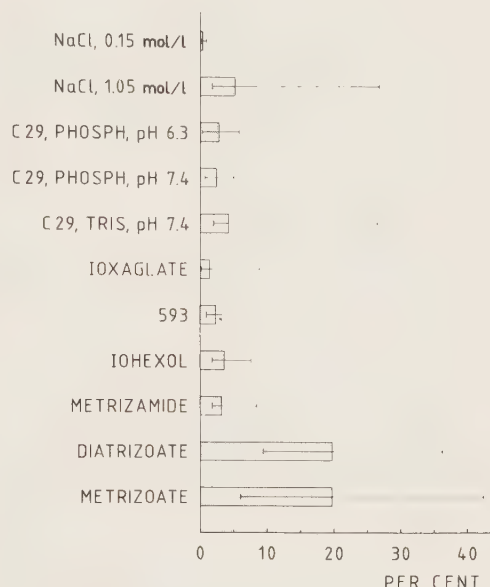


Fig. 3. Extent of endothelial injury caused by the different test solutions in per cent of the total vascular region examined. Median value and range are given.

trizamide, ioxaglate and sodium chloride, substance concentration 1.05 mol/l.

Discussion

Silver staining technique. GOTTLOB & HOFF (1968) suggested that silver staining of endothelium occurs in two stages. First polyanions, probably acid mucopolysaccharides, located primarily in the intercellular gaps bind and reduce silver ions forming a network of metallic silver grains, that are invisible in a light microscope. Chloride ions in the tissue also bind and precipitate silver ions. In the second stage light reduces the silver ions in silver chloride resulting in a visible aggregation of metallic silver around the silver grains reduced during the first stage. According to FLOREY et coll. deposition of silver granula occurs in the spaces between cells, over their surface and to a variable distance into adjacent cytoplasm. Therefore, silver staining of normal vascular endothelium does not exactly delineate cell membranes or the intercellular spaces but gives in a light microscope the illusion of solid intercellular lines.

Chemical and physical trauma to vascular endo-

thelium may result in increased permeability or desquamation of endothelial cells, which permits the silver nitrate solutions to penetrate and stain subendothelial structures (O'NEILL 1947, SAMUELS & WEBSTER, ROBERTSON et coll. 1959, HOFF & GOTTLÖB 1967). ROBERTSON et coll. found that the transverse lines in injured areas represented silver accumulation between smooth muscle cells of the media. The injured areas often have a patchy distribution and a tendency to be localized in narrow bands oriented along the long axis of the vessel (HOFF & GOTTLÖB). This was also observed in the present experiments. The method used in the present material has the advantage of allowing perfusion and prefixation of the specimen in situ without touching it. Work of ROBERTSON et coll. indicates that even minor trauma to the exterior of the vessel may cause endothelial injury. However, the manual injections of the various solutions may cause pressure variations. According to AUSMAN et coll. variation of the pressure between 50 and 250 mm Hg or intermittent flow should not have any injuring effect on endothelium as evidenced by the silver staining technique. The silver nitrate solution may per se be noxious to endothelium (WILLIAMS & MONTGOMERY 1959) and, depending on application time and perfusion pressure, result in subendothelial silver staining (GOTTLÖB & HOFF 1967).

The incidence of subendothelial silver staining following injection of isotonic sodium chloride was low (median value 0.2%). This indicates that the preparation of the aorta per se had no major endothelial injuring effect relative to that of the contrast media and hypertonic sodium chloride, which caused significantly greater changes.

Effects of contrast media. Endothelial injury following application of non-ionic and ionic monomers for 5 min on the rat aortic endothelium was examined with silver staining technique in male rats by RAININKO (1979a) and in the present experiments, in female rats by ALMÉN et coll. (1973, 1975) and ALMÉN & ASPELIN (1975). The relative size of the injured areas caused by the various agents was similar in all reports but the extent of changes was considerably less in the work of RAININKO (1979a) than in the other experiments. The reason for this difference is not known since the same preparation technique seems to have been used. The present results are in agreement with those of AUSMAN et coll. who injected sodium diatrizoate (Hypaque 50%, 300 mg l/ml) with an application time of 1.5 to

2.0 min resulting in 11 per cent changes in rat aortic endothelium. It might be worth noting that ether and pentobarbital were used for anaesthesia in all experiments except those of RAININKO (1979a), who used pentobarbital only.

In the present experiment non-ionic monomeric and monoacidic dimeric contrast media caused significantly less subendothelial silver staining than the ionic monomers. This is in accordance with previous animal experiments. ALMÉN et coll. (1973, 1975) and ALMÉN & ASPELIN found that metrizamide was less harmful to rat aortic endothelium than metrizoate. GONSETTE (1978) observed that ioxaglate had a very mild effect, of the same magnitude as isotonic saline, on carotid endothelium in guinea pigs. The ionic monomers have an osmolality that is significantly higher than that of non-ionic monomers and monoacidic dimers. The difference in osmolality is explained by the fact that at equal iodine concentrations the relation between the number of iodine atoms and the number of particles in an ideal solution is less for ionic monomers (ratio $3/2=1.5$) than for non-ionic monomers (ratio $3/1=3.0$) and monoacidic dimers (ratio $6/2=3.0$). No significant difference was found between the various contrast media with a ratio of 3.0 in their endothelial injuring effect, nor any difference between the two contrast media with a ratio of 1.5. The difference between the contrast media with a ratio of 1.5 and 3.0 might therefore be explained by the difference in osmolality.

Role of osmolality. Injection of sodium chloride in concentrations equiosmolal to the contrast media with a ratio of 1.5 caused less changes than these media, but the degree of change was insignificantly different from that produced by the contrast media with a ratio of 3.0. The extent of endothelial injury caused by contrast medium solutions must therefore also be determined by other factors than osmolality. This is in agreement with previous experiments using the silver staining technique to disclose endothelial injury (ZINNER & GOTTLÖB, MCCONNELL & MERSEREAU, ALMÉN & ASPELIN, RAININKO 1979b), and with experiments regarding the effect on permeability in the blood-brain barrier (BROMAN & OLSSON 1949, BASSET et coll. 1953, HOPPE 1959, WALDRON et coll. 1974), glomeruli of the kidney (HOLTÅS et coll. 1978) and hamster cheek pouch (SÖRENSEN 1971).

pH and buffer. The decrease in pH from 7.4 to 6.3 in the C29 solution in the present experiments had

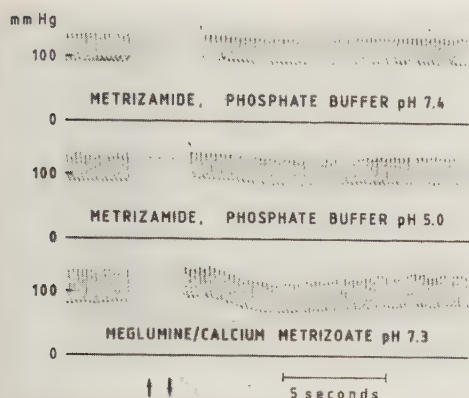


Fig. 3. Recordings of aortic blood pressure before and after injection of various contrast media into the aorta. Time of injection (1 s). Start ($\uparrow$), end ($\downarrow$) of injection.

Viscosity. Microcirculatory investigations indicate that the high viscosity of contrast media compared with sodium chloride solutions may play some role when evaluating the difference in hemodynamic response (SØRENSEN & ASANO 1971, EKELAND & UFLACKER 1978). According to these authors intraarterial bolus injections of contrast medium solutions and sodium chloride give a short period of ischemia during their passage through the peripheral vascular bed. The duration of the ischemic or passage time was significantly longer for contrast media than for iso- and hypertonic solutions of sodium chloride, a difference that might be related to the higher viscosity of the contrast medium solutions. This would mean an increased application time for the contrast media during which they can exert their osmotic and possible chemotoxic effects. In addition the ischemic effect per se of an injected bolus may contribute to the decrease in vascular resistance. A reactive hyperemia following the ischemic period would then be more marked after injection of contrast media than after sodium chloride. Thus, the difference in hypotensive reaction noted in the present experiments between contrast media and equiosmolal solutions of sodium chloride may theoretically be explained by a chemotoxic effect of the iodinated organic molecule or by the higher viscosity of the contrast media.

The pH of the solution must also be considered when evaluating the effect on the peripheral vascular resistance. It is known that solutions both on the acid and alkaline side of the physiologic pH-

range have vasodilatory properties (ELLIOTT & JASPER 1949, KESTER et coll. 1952, DEAL & GREEN 1954, HADDY et coll. 1958). Both the present and previous results (ALMÉN 1973a) indicate that progressive alteration of the pH below 7.4 of non-ionic contrast media will increase the fall in aortic blood pressure.

According to KESTER et coll. injections of buffered acid and alkaline solutions of sodium chloride produce a decrease in peripheral vascular resistance while variation of pH of unbuffered solutions of sodium chloride do not. The difference in hypotensive effect between injections of buffered solutions of metrizamide and C29 at pH 5.0 compared with injection of the same solutions at pH 7.3 to 7.4 was therefore expected. However, metrizamide adjusted to pH 5.0 by adding hydrochloric acid, an unbuffered solution, produced the same decrease in blood pressure as a buffered solution of metrizamide at the same pH. While KESTER et coll. injected 1 ml of sodium chloride during 10 s into the femoral artery in dogs, 2 ml during 1 s was injected into the aorta in rabbits in the present experiments. These differences in methods cannot explain the hypotensive effect of unbuffered solutions of metrizamide at pH 5.0, since injections of unbuffered equiosmolal solutions of sodium chloride at pH 5.5 did not produce any fall in aortic blood pressure. One explanation may be that the ability of blood to buffer unbuffered acidic solutions of contrast media may be counteracted by their high viscosity, which delays the mixing of blood and contrast media. The unbuffered contrast media may thus still possess their acidic properties when reaching the peripheral vascular bed.

Injections of metrizamide and C29 at pH 7.3 to 7.4 with the use of phosphate, TRIS and bicarbonate as different buffering systems did not cause any difference in hypotensive reaction.

Conclusions

Contrast medium solutions for peripheral angiography should have an osmolality and a pH close to that of human plasma in order to minimize the risk of fall in arterial blood pressure. The choice of buffer (phosphate, TRIS and bicarbonate), in order to give the solutions a proper pH, seems to be of minor importance.

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pH and buffer. The decrease in pH from 7.4 to 6.3 in the C29 solution in the present experiments had

no influence on the degree of subendothelial staining. Furthermore, no difference was found between C29 solution with phosphate or TRIS buffer. However, this does not exclude a potential toxic effect of the buffers used since they were not analysed separately from the contrast medium solutions.

Chemotoxicity and other factors. The relative role of the chemical structure of the iodinated molecule, the composition of the cations of the ionic media and the viscosity of the contrast medium solutions cannot be evaluated from the present experiments.

MCCONNELL & MERSEREAU stated that the viscosity of ionic monomeric solutions does not appear to be an important factor and ZINNER & GOTTLÖB claim that the high viscosity of contrast media rather has a protective effect.

RAININKO (1979a) reported that among pure meglumine salts of ionic monomers, iothalamate was the most injuring one, followed by iodamide and metrizoate (with a small amount of calcium), which in turn were more injuring than diatrizoate. She found no difference between diatrizoate and metrizamide. This is contradictory to the present results, in which no difference was observed between diatrizoate and metrizoate, both containing a mixture of the meglumine and sodium salt in similar proportions. MCCONNELL & MERSEREAU, who also examined the effect of cations, found that the toxicity in descending order of different diatrizoate and iothalamate solutions on silver stained carotid endothelium in rabbits was: (1) meglumine diatrizoate, (2) meglumine iothalamate and sodium iothalamate, and (3) sodium diatrizoate. From these conflicting results it may be speculated whether added preservatives or impurities due to various laboratory and manufacturing techniques may have any influence. A toxic effect of calcium chelating agents in contrast media has recently been reported by VIOLANTE et coll. (1978) who found that they increase the risk for ventricular fibrillation in coronary angiography. Depletion of calcium ions by chelating agents may affect the integrity of cell to cell attachment (BORYSENKO & REVEL 1973, ROSE et coll. 1977), which theoretically might be one explanation for the penetration of silver to underlying structures caused by certain contrast medium solutions.

Comparison with other types of endothelia. The relative mild toxic effect of metrizamide and ioxaglate relative to ionic monomeric contrast media on vascular endothelium has also been documented in

the blood-brain barrier (SALVESEN 1973, GONSETTE). C29 has been found to be even less harmful than metrizamide on the blood-brain barrier (GOLMAN 1979). HOLTÅS & TEJLER (1979) reported that C29 also produced less albuminuria, indicating increased glomerular permeability, following nephroangiography than metrizamide, which was as toxic with relevance to this parameter as meglumine/sodium diatrizoate. This indicates that no general conclusion can be drawn about the toxicity of a contrast medium from one type of vascular endothelium to another or that the results from various vascular regions differ depending on the method used.

Thrombus formation. Administration of contrast media has been demonstrated to decrease coagulation activity (BJÖRK 1968), reduce the concentration of coagulation factors (STEIN & HILTGARTNER 1968) and inhibit platelet aggregation (ZIR et coll. 1974). Thrombotic complications of contrast media are therefore probably due to a local endothelial injury with secondary inflammatory reaction. The type of injury occurring in the present experiments has been associated with thrombus formation (MERSEREAU & ROBERTSON, ROBERTSON et coll.). The observation that metrizamide causes less subendothelial silver staining than metrizoate corresponds well with clinical reports (ALBRECHTSSON & OLSSON 1979), which indicate that the risk for thrombosis after phlebography is less with metrizamide than with metrizoate.

Conclusion

The new non-ionic monomeric (C29, 593 and io-hexol) and monoacidic dimeric (ioxaglate) contrast media seem to have a potential advantage over currently used ionic monomeric contrast media for angiography and phlebography since they induce less endothelial injury as evaluated with this silver staining method. They also have the advantage over metrizamide that they tolerate autoclaving.

SUMMARY

Injury to the aortic endothelium in rats was evaluated under a light microscope by a silver staining method after application of ionic monomeric (diatrizoate and metrizoate), non-ionic monomeric (C29 with different pH and buffers, 593, io-hexol and metrizamide) and monoacidic dimeric (ioxaglate) contrast media, and iso- and hypertonic solutions of sodium chloride. In iodine equivalent

concentrations the ionic monomers were significantly more toxic than the other contrast media. No significant difference was found between the non-ionic monomers, monoacidic dimer and sodium chloride solutions equimolar to the ionic monomers. Isotonic saline was the least harmful solution.

ACKNOWLEDGEMENTS

This investigation was supported by a grant from the Swedish Medical Research Council (Project No. 3483). The expert technical assistance of Gail Åkerman is gratefully acknowledged.

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PAIN AND HEMODYNAMIC EFFECTS IN AORTOFEMORAL ANGIOGRAPHY

Clinical comparison of iohexol, ioxaglate and metrizamide

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An ideal contrast medium for angiography of extremity arteries should not produce any pain, hemodynamic effects or other adverse reactions. The contrast media commonly used for these procedures are ionic monomeric compounds such as diatrizoate, iothalamate and metrizoate which have an osmolality 5 to 7 times that of human plasma. These compounds cause pain and a decrease in vascular resistance down-stream to the site of injection resulting in increased blood flow and decreased arterial blood pressure (DELIUS & ERIKSON 1969, BOIJSEN et coll. 1971). The sensation of pain and hemodynamic effects were considerably less when metrizamide (Amipaque), a non-ionic monomeric contrast medium, was introduced for aortofemoral angiography (ALMÉN et coll. 1977, ANDREW et coll. 1981).

The non-ionic monomeric iohexol (Nyegaard & Co., Oslo) and the monoacidic dimeric ioxaglate (Hexabrix, Laboratoire Guerbet, Paris) are newly developed iodinated water-soluble contrast media that have been approved for clinical angiographic trials. Metrizamide, iohexol and ioxaglate have in iodine equivalent concentrations less than half the osmolality of the ionic monomeric compounds. Contrary to metrizamide, iohexol and ioxaglate tolerate autoclaving. They can therefore be supplied as sterile solutions and the expensive process of sterile filtration and freeze-drying necessary for metrizamide is avoided.

Animal experiments have demonstrated that injections of iohexol and ioxaglate into the aorta and femoral arteries produced significantly less decrease in vascular resistance than the conventional ionic compounds, while no difference between iohexol, ioxaglate and metrizamide was found (AMIEL et coll. 1978, NYMAN et coll. 1980 a, b, STEINER et coll. 1980).

Clinical trials with ioxaglate in aortofemoral angiography have shown that it induces significantly less decrease in systemic blood pressure (HOLM & PRAESTHOLM 1979) and less sensation of heat and pain (GRAINGER 1979, HOLM & PRAESTHOLM, TILLMANN et coll. 1979). In one investigation these effects of ioxaglate were equal to those of metrizamide (ZACHRISSON et coll. 1980). Van WAES (1979) reported serious subjective reactions after 22 per cent

of the injections with ioxaglate, but none after metrizamide. Recently PRAESTHOLM et coll. (1981) found iohexol to produce less decrease in blood pressure and less pain than diatrizoate during angiography of the lower limbs.

An evaluation of the effects of iohexol and ioxaglate during aortofemoral angiography in comparison with those of metrizamide was performed. This was done by recording blood flow, aortic blood pressure, ECG and patient reactions; in addition patient reactions to metrizoate (Isopaque Cerebral, Nyegaard & Co.) were recorded. The results are now reported.

MATERIAL AND METHODS

Contrast media. The composition, concentration, osmolality and viscosity of the contrast media used, volumes injected and rate of injection are given in Table 1.

Study design. In a single blind randomized study the effects of one injection of iohexol and one of metrizamide into the distal aorta of the same patient were compared in one group of patients. In another group ioxaglate was compared with metrizamide in the same way. In both groups a subsequent injection of metrizoate was made and the patient reactions recorded.

Patient material. Forty patients referred for aortofemoral angiography because of symptoms of obliterative arterial disease were selected. Group 1 consisted of 4 women and 16 men, aged 48 - 74 years (median age 62 years) and group 2 of 7 women and 13 men, aged 47 - 76 years (median age 61 years). Patients with poor general condition, diabetes, reduced renal function (serum creatinine level above 115 $\mu\text{mol/l}$) or lower extremity neuropathy were excluded. Informed consent was obtained from each patient.

Angiographic procedure. The patients were orally premedicated with 10 mg of diazepam (Apozepam, A/S Apothekernes Laboratorium, Oslo) about one hour before the examination. The femoral artery was percutaneously catheterized after local anesthesia, and a

Table 1

Some chemical and physical properties of the contrast media used

	Metrizamide	Iohexol	Ioxaglate [*]	Metrizoate
Iodine conc. mg/ml	300	300	300	280
Substance conc. mol/l	0.79	0.79	0.39	0.73
Calcium salt (mol/l)	-	-	-	0.009
Sodium salt (mol/l)	-	-	0.14	-
Meglumine salt (mol/l)	-	-	0.25	0.72
Sodium bicarb. (mol/l)	0.0006	-	-	-
TRIS (mol/l)	-	0.01	-	-
Osmolality (mol/kg H ₂ O)	0.45 ^{**}	0.69	0.55	1.46
Viscosity (20 ^o , mPa·s)	12.7 ^{**}	11.6	12.5	7.1
Inj. volume (ml)				
group 1	45	45	-	45
group 2	50	-	50	30
Inj. rate (ml/s)				
group 1	12	12	-	12
group 2	12	-	12	15 - 20

* Hexabrix 32 % diluted by distilled water

** Estimated by interpolation

The values of concentration, osmolality and viscosity are given by the manufacturers.

pigtail polyethylen catheter (OD/ID 2.2/1.45 mm, six sideholes, length 80 cm) was advanced to the level of the renal arteries. Intra-arterial heparinization with 30 IU/kg body weight was performed. All contrast media were injected with an automatic injector (Mark IV, Medrad), at room temperature and with an interval of at least 10 min. The first injection was made with 30 ml of metrizoate to obtain a lumbar aortography. The catheter was then placed with its tip 4 to 5 cm above the aortic bifurcation, where the second and third injections in group 1 were made with iohexol and metrizamide, and in group 2 with ioxaglate and metrizamide with the patient in supine position. With the catheter in the same position additional injections for oblique projections were performed with metrizoate. This was made in all patients but one.

Patient reactions. After the second, third and fourth injection every patient was asked if he had experienced any heat, pain or any other sensation by using a standardized questionnaire. The degree of heat and pain was marked by the patient on a visual analogue scale (OHNHAUS & ADLER 1975, TILLMANN et coll.). On this scale the left end of a 100 mm long line signified no heat or pain and the right end unbearable heat or pain. The distance in millimeters from the left end of the line to the patient's marking was measured. One scale for heat and one for pain were used for all three injections. The patients were also observed for any other reaction during and after the examinations.

Hemodynamic measurements. Blood flow, mean aortic pressure and heart rate were recorded in 10 patients in each group after injection of iohexol or ioxaglate and metrizamide (injection 2 and 3). Patients with pain at rest were excluded.

Blood flow was measured with strain gauge plethysmography using electrical calibration (DAHN & HALLBÖÖK 1970, HALLBÖÖK et coll. 1970). The feet were elevated approximately 15 cm above the table. A strain gauge was placed around the thickest part of each calf and the occlusive cuffs immediately above the knees. The venous occlusion pressure was 60 mm Hg. The preinjection blood flow was calculated from the mean value of 4 plethysmographic measurements. Following the injections measurements were performed every 20 s

for approximately 3 min with the first recording 30 s after the start of injection.

Mean aortic blood pressure was recorded before and after the injections through the angiographic catheter, which was connected to a pressure transducer (Bentley Trantec Inc., Irvine) via a three-way stopcock. The pressure recordings were interrupted from a few seconds before the injection until 5 to 10 s after the start of the injection. All hemodynamic parameters including a precordial ECG were recorded on a Mingograf (Siemens-Elema). The heart rate (beats/min) was calculated from 10 beats about 15 s after the start of injection and then simultaneously with the plethysmographic recordings.

Simultaneously obtained mean aortic pressure and blood flow registrations were used for calculation of peripheral vascular resistance. Total vascular resistance was defined as the quotient between mean aortic pressure and the sum of blood flow in both calves and was calculated for each recording period. Total vascular resistance at each recording after the injection was then expressed in per cent of the total resistance before the injections.

The correlation between the changes in vascular resistance caused by the contrast media and the degree of arterial disease in single legs in both groups was also noted. The degree of disease was based upon ankle index values (ankle blood pressure/arm blood pressure) obtained from the routine clinical physiologic examinations of these patients before angiography. Nine legs with an ankle index close to the lower limit 1.0 (range 0.91 - 1.15, median value 1.03) represented the least diseased group and 9 with the lowest index (range 0.32 - 0.52, median value 0.48) the most diseased. In the least diseased group proximal artery stenosis and symptoms of claudication were present in two legs, while in the most diseased group all had major artery occlusions with collateral circulation and claudication.

Vascular resistance of a single leg was calculated in the following way: The quotient between aortic pressure and calf blood

flow of that leg was calculated for each recording period before and after the 2nd and 3rd contrast medium injection. The mean value of the quotients obtained before the two injections represents the vascular resistance of that leg before injection. The mean value of the quotients obtained during the 1st registration period after the 2nd and 3rd injection represents the vascular resistance of that leg during that period. Similar calculations were made for each of the consecutive recording periods after injection. Vascular resistance of a single leg at each recording period after injection was then expressed in per cent of the resistance before injection.

Statistics. Wilcoxon's test for pair differences was used for statistical analysis of the changes in blood pressure, heart rate, total vascular resistance, and of heat and pain sensation. Mann-Whitney's test for unpaired data was used when changes in vascular resistance in the least and most diseased legs were compared. p-values of 0.05 or less were considered significant.

RESULTS

Patient reactions

The number and types of adverse reactions induced by the contrast media are summarized in Fig. 1 and Table 2.

Heat. A sensation of heat was experienced by all patients after each contrast medium injection. The degree of heat was significantly greater after metrizoate than after metrizamide, iohexol and ioxaglate, but the latter three media did not differ significantly.

Pain. Five patients experienced pain after injection of iohexol but not after metrizamide. The opposite reaction occurred in one patient. On two occasions when both contrast media caused pain iohexol was more painful. Two patients complained of pain after ioxaglate but not after metrizamide, while in one the degree of pain was equal. The degree of pain induced by iohexol and ioxaglate did not differ significantly from that of metrizamide. On those occasions when these contrast media caused pain, it was

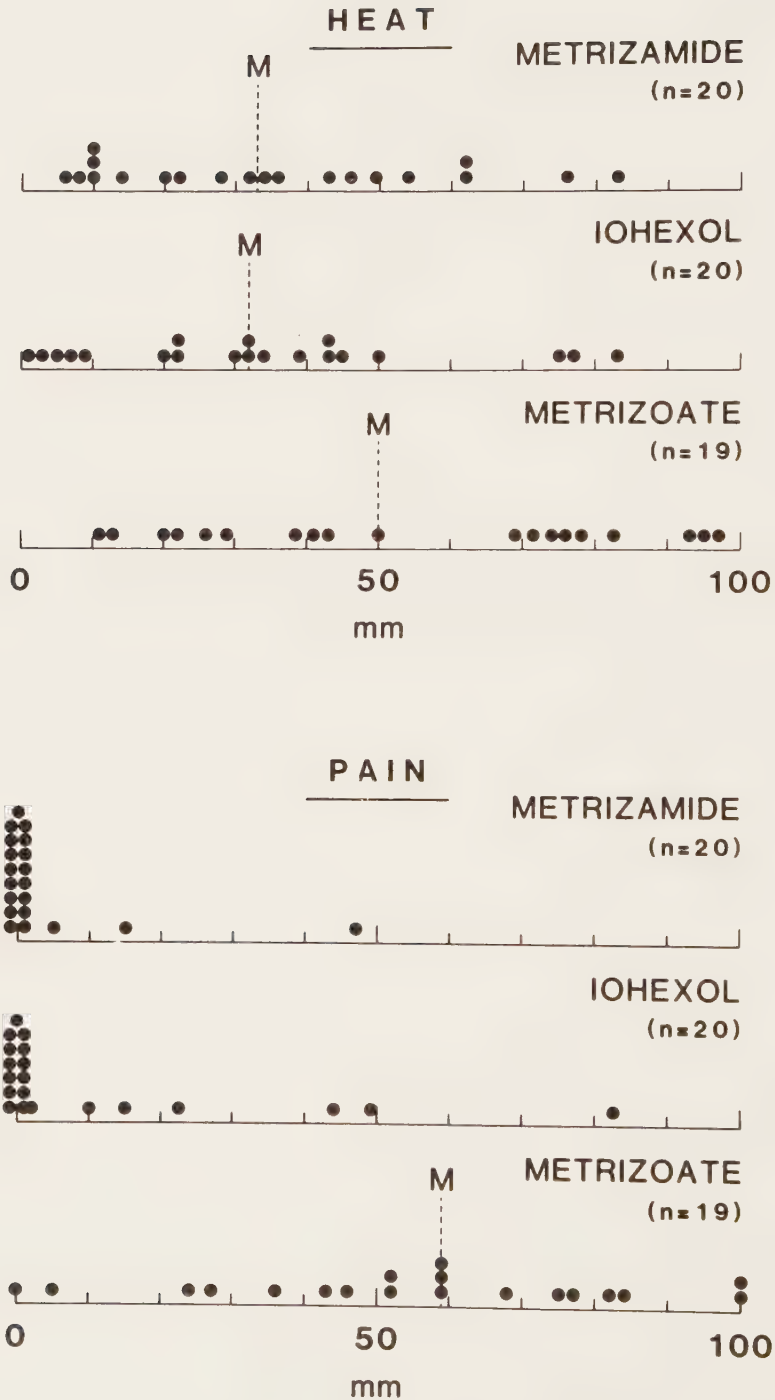


Fig. 1a. The degree of heat and pain marked by the patients on a visual analogue scale (Group 1).

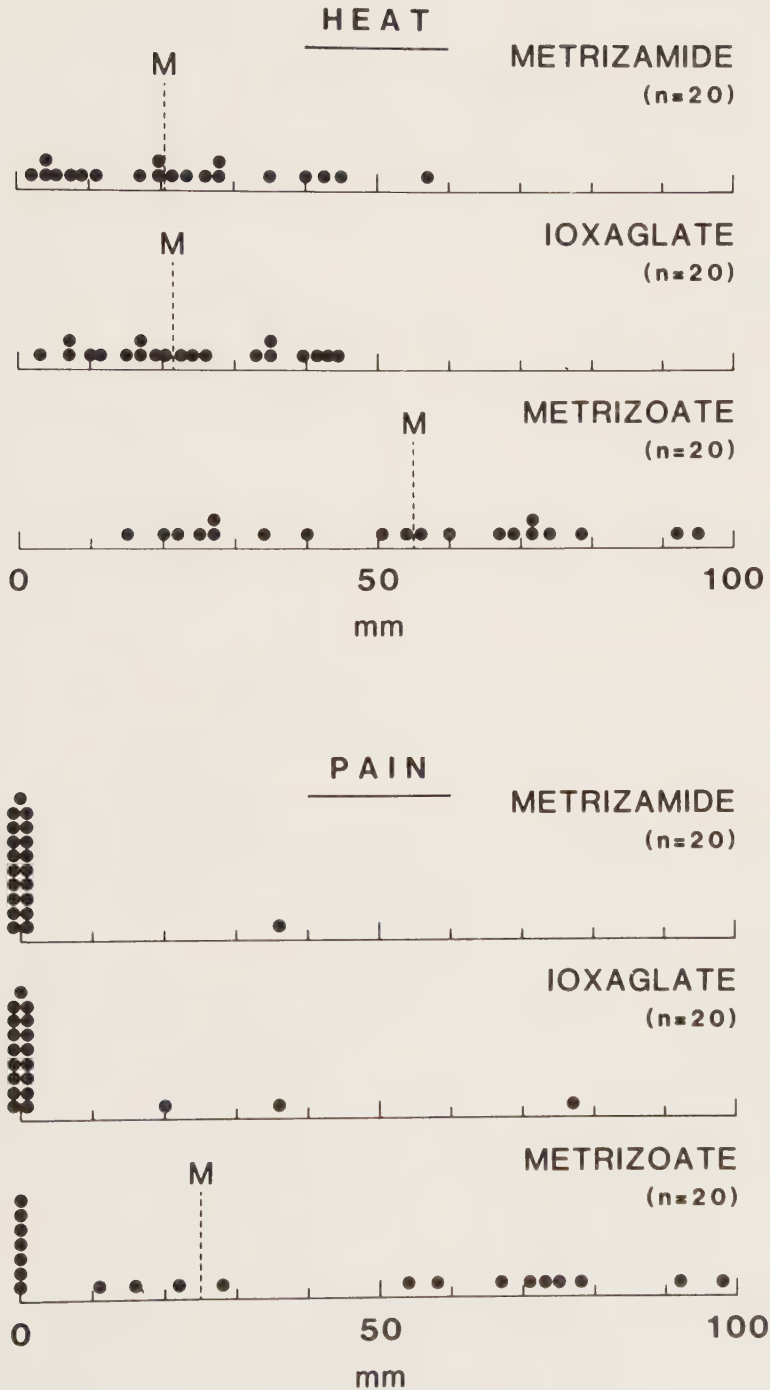


Fig. 1b. The degree of heat and pain marked by the patients on a visual analogue scale (Group 2).

Table 2

Number of patients with adverse reactions in
aortofemoral angiography

Contrast medium	Heat	Pain	Nausea	Urticaria
Group 1				
Metrizamide (N=20)	20	3	0	0
Iohexol (N=20)	20	7	1	0
Metrizoate (N=19)	19	18	0	0
Group 2				
Metrizamide (N=20)	20	1	0	0
Ioxaglate (N=20)	20	3	3	1
Metrizoate (N=20)	20	13	0	0

always less than the pain evoked by the subsequent injection of metrizoate. There was a significant difference between metrizoate and the other three compounds according to the degree of pain.

Observed reactions. Urticaria in the face occurred in one patient after an injection of ioxaglate. Hydrocortisone phosphate was injected intravenously. The reaction had subsided before the next injection of contrast medium. Nausea occurred in three patients and two of them vomitted after injection of ioxaglate. One patient felt nausea after iohexol. No other adverse reactions were observed.

Hemodynamic effects

The time-related changes in total vascular resistance, blood pressure and heart rate are illustrated in Fig. 2. The blood flow increased significantly, mean aortic pressure decreased and heart rate increased following injection of all the tested solutions (metrizamide, iohexol and ioxaglate). The maximum changes

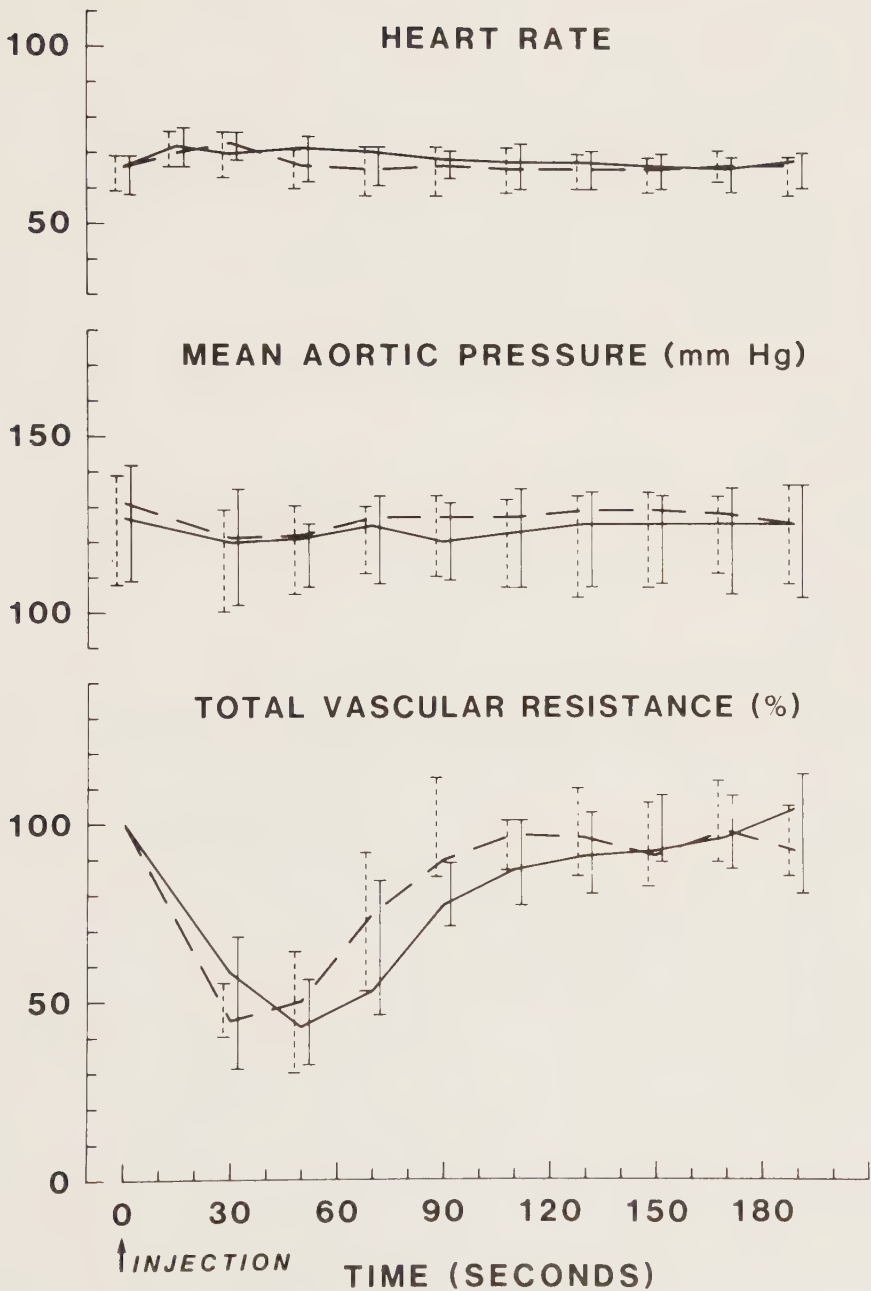


Fig. 2a. Hemodynamic effects of metrizamide (—) and iohexol (---). The curves represent median value with interquartile range outlined.

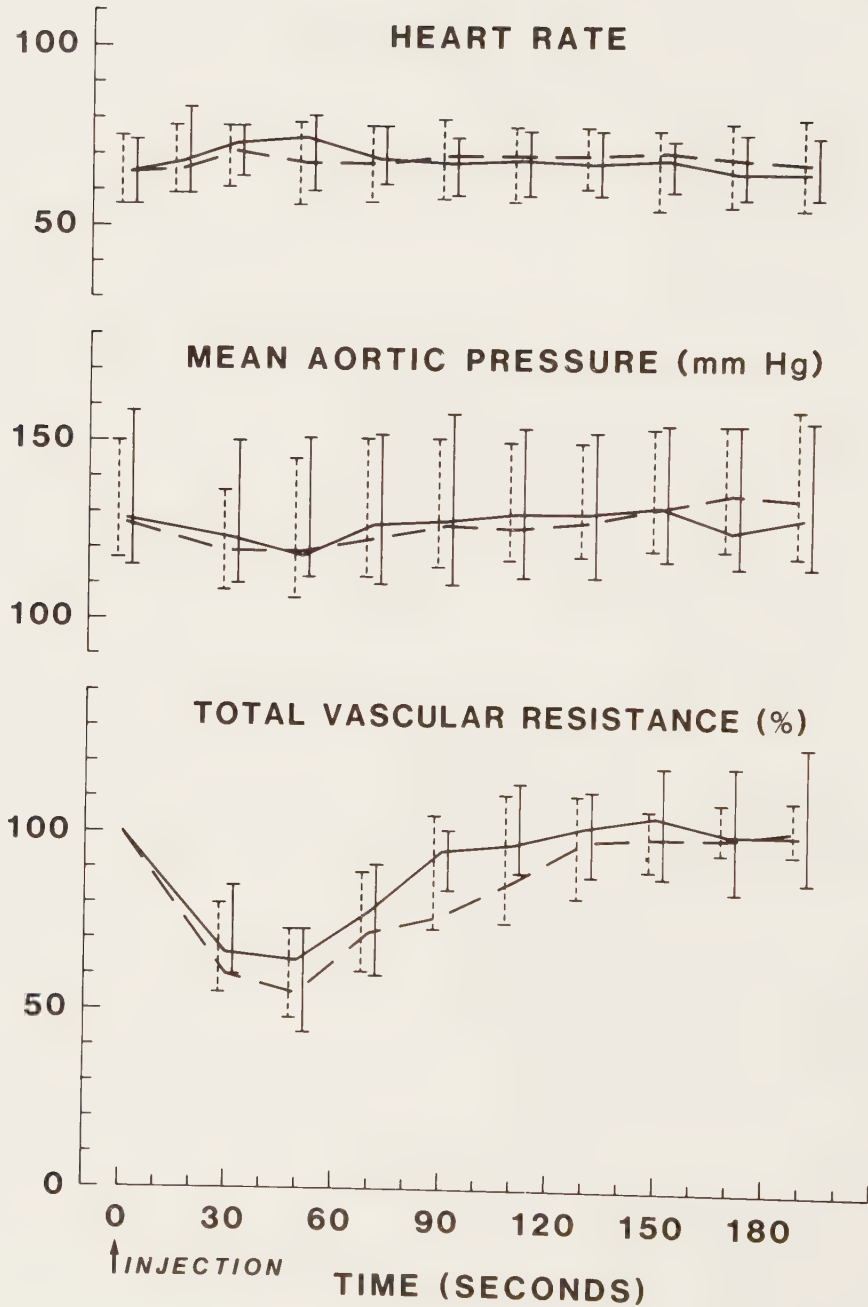


Fig. 2b. Hemodynamic effects of metrizamide (—) and ioxaglate (---). The curves represent median value with interquartile range outlined.

of these parameters (Table 3) occurred at the 30 and 50 s recordings.

Vascular resistance. The total vascular resistance decreased approximately 50 per cent (median value) at the 30 and 50 s recordings after injection of all three contrast media. After 2 min the resistance values had returned to the preinjection level. No significant difference was found between metrizamide and ioxaglate regarding the effect on total vascular resistance. Nor was there any difference between metrizamide and iohexol except that metrizamide caused significantly lower resistance at the 90 s recordings.

The changes in total vascular resistance that occurred after the second injection of contrast medium were compared with those after the third injection in all 20 patients. This comparison did not yield any significant difference.

The changes in vascular resistance that occurred in the least and most diseased legs are illustrated in Fig. 3. No significant difference existed between the two groups except that the group of most diseased legs showed significantly less decrease in resistance at the 30 s recordings.

Blood flow. The blood flow increased in both calves in all but 2 patients after the injections. In these two patients calf blood flow decreased in one of the legs after both injections. Long occlusion of the iliac artery with sparse collaterals supplying these legs were present, while in both cases no occlusion or stenosis in the contralateral leg existed. The most prominent decrease of blood flow in one of the patients lasted for 1.5 min with a maximum decrease of 90 per cent while the corresponding figures for the other patient were 3 min and 42 per cent.

Aortic pressure and heart rate. The median value of the maximum fall in mean aortic pressure was approximately 10 mm Hg for all three compounds. In one patient the maximum fall reached 30 mm Hg. No arrhythmia was noted except for a short-lasting bradycardia in one patient after an injection of iohexol, which contributed to

Table 3

Median (and range) of hemodynamic parameters before injection and maximum changes after injection of the various contrast media

HEART RATE (beats/minute)		
	Before injection	Maximum increase
Metrizamide (N=20)	66 (50 - 83)	7 (3 - 20)
Iohexol (N=10)	65 (55 - 80)	8 (2 - 18)
Ioxaglate (N=10)	65 (50 - 80)	6 (3 - 15)

MEAN AORTIC BLOOD PRESSURE (mm Hg)		
	Before injection	Maximum decrease
Metrizamide (N=20)	128 (101 - 180)	9 (0 - 20)
Iohexol (N=10)	131 (100 - 152)	12 (2 - 26)
Ioxaglate (N=10)	127 (105 - 175)	10 (0 - 30)

ARTERIAL BLOOD FLOW IN INDIVIDUAL LEGS (ml/min x 100 ml tissue)		
	Before injection	Maximum increase
Group 1		
Metrizamide (N=20)	2.7 (1.7 - 5.6)	4.4 (0.7 - 7.5)
Iohexol (N=20)	2.6 (1.6 - 4.8)	4.8 (-0.4 - 8.0)
Group 2		
Metrizamide (N=20)	3.9 (1.9 - 8.8)	3.6 (0 - 7.8)
Ioxaglate (N=20)	4.2 (1.4 - 8.4)	2.9 (0.8 - 6.4)

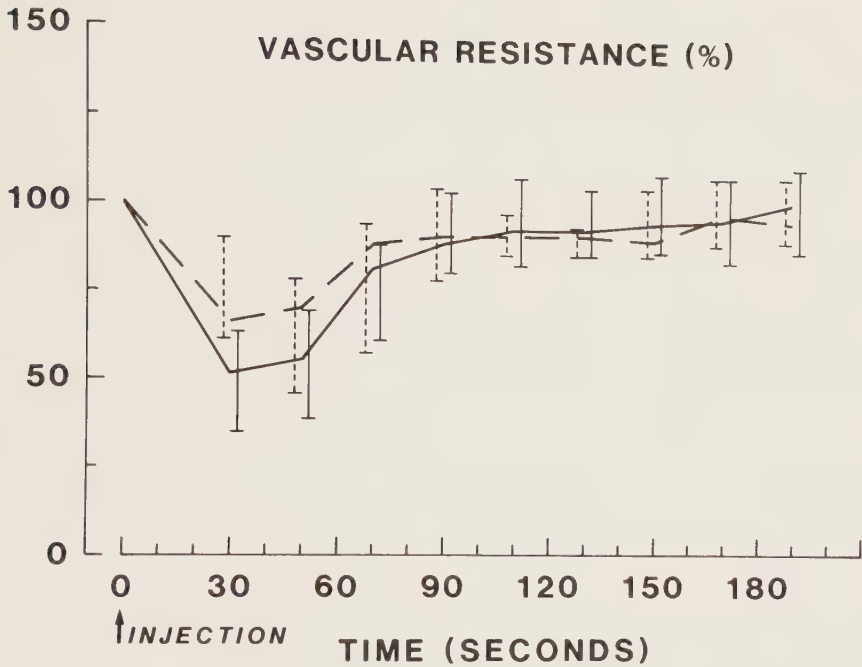


Fig. 3. Effect on peripheral vascular resistance in least diseased (—) and most diseased (---) legs. The curves represent median value with interquartile range outlined.

the fall in blood pressure. The median value of the maximum increase in heart rate was about 7 beats/min for all contrast media. The maximum increase in one patient was 20 beats/min. The effects on aortic pressure and heart rate caused by the various contrast media did not differ significantly.

Diagnostic information

The solutions of iohexol and ioxaglate were injected with the same volume, rate and iodine concentration as metrizamide. The solutions had about the same viscosity. As could be expected the diagnostic quality as evaluated from the demonstration of individual arteries and pathological lesions was the same for iohexol, ioxaglate and metrizamide. No comparison was made with metrizoate since it was used only for oblique projections.

DISCUSSION

The development of contrast media from the aqueous solution of sodium iodide used by BROOKS (1924) to the currently used tri-iodinated monomeric derivatives of benzoic acid has resulted in a tenfold decrease in systemic toxicity as evaluated by intra-venous LD₅₀ (HOPPE et coll. 1967). The systemic toxicity of metrizamide (SALVESEN 1973) and ioxaglate (Report issued by Laboratoire Guerbet) has been found to be approximately half that of the ionic monomeric compounds. Iohexol seems to have an even lower toxicity than metrizamide (SALVESEN 1980).

Injections of ionic monomeric contrast media and other hypertonic solutions into the aorta and extremity arteries produce a fall in peripheral vascular resistance due to vasodilatation which results in increased blood flow and decreased systemic blood pressure accompanied by an increase in heart rate. This has been demonstrated in both animals (MARSHALL & SHEPHERD 1959, OVERBECK et coll. 1961, HILAL 1966, LINDGREN et coll. 1967, EFSSEN & MUNKNER 1968) and man (DELIUS & ERIKSON, OVERBECK & GREGA 1970, BOIJSEN et coll.). These vascular reactions were significantly reduced when metrizamide was used instead of the ionic monomeric compounds (ALMÉN 1973, ALMÉN & TRÄGÅRDH 1973, ALMÉN et coll., NYMAN & ALMÉN 1978) which has been attributed to the marked difference in osmolality between these contrast media.

Metrizamide and ioxaglate have about the same osmolality and caused similar hemodynamic changes during aortofemoral angiography in the present series, which is in agreement with the results of ZACHRISSON et coll. and previous animal experiments (NYMAN et coll. 1980 a, b). The hemodynamic effects caused by iohexol were also equal to those of metrizamide, though iohexol has a higher osmolality than metrizamide. In animal experiments sodium chloride solutions in equiosmolal concentrations with metrizamide produced no obvious effects on peripheral vascular resistance (NYMAN et coll. 1980 a, b). This means that the vasodilatory properties of metrizamide, iohexol and ioxaglate might be due to a chemotoxic effect, or that they can exert their osmotic effect during a longer time since contrast media appear to pass the

peripheral vascular bed more slowly than sodium chloride solutions (SÖRENSEN & ASANO 1971, EKELAND & UFLACKER 1978).

Using a technique similar to the present one, BOIJSEN et coll. observed an initial decrease in calf blood flow about 10 to 15 s after injections of metrizoate followed by a marked increase. No recording of blood flow was performed in the present series until 30 s after injection. Experiments by SCHRÖDER et coll. (1981) indicate that this initial decrease in blood flow is due to the viscosity of the contrast medium solutions, rather than to the blockade of capillaries and the increased whole blood viscosity that may result from the hypertonic and chemotoxic effects of contrast media on red blood cells (RAND & LACOMBE 1965, BROWN et coll. 1968, ASPELIN 1979, ASPELIN et coll. 1980 a). According to this explanation the initial decrease in blood flow noted by BOIJSEN et coll. might be larger with the low osmolality contrast media since they are more viscous than the ionic monomeric compounds. The unilateral decrease in calf blood flow lasting up to 1.5 and 3 min after injection that occurred in 2 patients is probably not explained by the factors mentioned. These 2 patients had unilateral iliac artery occlusions with sparse collaterals. Calf blood flow decreased in these legs with proximal occlusions possibly due to proximal steal.

The observation that no great difference occurred in the reduction of vascular resistance between least and most diseased legs has also been made by DELIUS & ERIKSON. The present series did not include any patient with ischemic pain and obviously the proximal occlusions were compensated by collaterals and the vasodilatory capacity of the peripheral vessels was preserved even in the most diseased legs.

The pain caused by the currently used ionic monomeric contrast media is a great discomfort to the patient during aortofemoral angiography and may also result in blurring of the films due to uncontrolled movements by the patient. The sensation of pain has to a large extent been attributed to the hypertonicity of these solutions (SPECK et coll. 1980, HOLDER & DALRYMPLE 1981). In order to reduce the pain, intra-arterial injection of lidocaine

(GORDON & WESTCOTT 1977, WIDRICH et coll. 1977), premedication with various drugs (GUTHANER et coll. 1977, SCHMIDT et coll. 1979) and even general anesthesia (HOLSTEN 1978) have been used. The effectiveness of lidocaine in reducing pain has been disputed by EISENBERG et coll. (1978) and the use of general anesthesia means an increased risk for the patients (ZEITLER 1978, BARTH & BRÄUTIGAM 1979).

Several clinical reports, as well as the present one, have stated that low osmolality contrast media such as ioxaglate, metrizamide, iohexol and another non-ionic monomer, iopamidol (Bracco, Milan) have markedly reduced the heat and pain sensation compared with that caused by ionic monomers (MEVES et coll. 1978, ALMÉN 1979, GRAINGER, HOLM & PRAESTHOLM, SCHMITT & Da SILVA 1979, TILLMANN et coll., ANDREW et coll., PARTRIDGE et coll. 1981, PRAESTHOLM et coll., FLETCHER 1982). In the present and other reports (ZACHRISSON et coll., MATHIAS et coll. 1981, WHITEHOUSE & SNOWDON 1981) no major difference was found regarding the pain-producing effect between various non-ionic contrast media or between ioxaglate and non-ionic media. Following intrafemoral injections of iohexol and metrizamide in unanesthetized rats no behavioural changes indicating pain were observed (SIEFERT et coll. 1980). The discrepancy found by van WAES between metrizamide and ioxaglate, with disadvantage to the latter, occurred when more selective angiographies were performed. With general use of the low osmolality compounds general anesthesia and intra-arterial lidocaine are not necessary for routine aortofemoral angiography.

The amount of contrast medium often used in aortofemoral angiography implies a certain risk for renal failure induced by the contrast medium, particularly in patients with one or more of the following risk factors: advanced age, pre-existing renal insufficiency, hypertension, diabetes mellitus and dehydration (BYRD & SHERMAN 1979). Iohexol and ioxaglate may have a potential advantage in this respect as renal hemodynamic changes are dependent on the osmolality of the solution (MORRIS et coll. 1978), and these media cause less morphological changes of red blood cells (ASPELIN et coll. 1980, MÜTZEL et coll. 1980), and less (in ani-

mals, HOLTÅS et coll. 1980, TÖRNQUIST et coll. 1980) or no post-angiographic proteinuria at all (in man, NILSSON et coll. 1982) compared with both metrizamide and ionic monomers. These advantages might be counteracted by the fact that iohexol and ioxaglate appear more concentrated in urine (SJÖBERG et coll. 1980) than ionic monomers, which might increase their toxic effects on tubular cells. SKALPE & EVENSEN (1973) found that metrizamide and metrizoate caused the same increase in mitotic rate in tubular cells.

Endothelial injury caused by contrast media has been discussed as a factor contributing to occlusion of stenotic vessels that may occur after aortofemoral angiography (MAY & NISSEL 1969, van ANDEL 1980). Iohexol, ioxaglate and metrizamide were found to induce less endothelial injury on rat aorta than diatrizoate and metrizoate (NYMAN & ALMÉN 1980).

A rare but severe complication of aortography is spinal cord damage which may result in paraplegia and even the patient's death (EFSSEN 1966, BROY 1971, Di CHIRO 1974). Contrast medium-induced rigidification of the red blood cells (ASPELIN 1979) resulting in decreased spinal cord circulation (MARGOLIS et coll. 1959) and thereby also an increased exposure time of the neurotoxic contrast media are among factors that may be responsible for such lesions. The risk for spinal cord lesions might be less with iohexol and ioxaglate as the rigidification of erythrocytes decreases with decreasing osmolality of the contrast medium solutions (ASPELIN et coll. 1980 b). Furthermore, the effect of iohexol and ioxaglate on the blood brain barrier is far less than that of the ionic monomeric compounds and comparable to the effect of metrizamide (GONSETTE 1978, AULIE 1980), while iohexol seems to be better but ioxaglate less well tolerated than metrizamide after application in the subarachnoid space (GONSETTE, GOLMAN et coll. 1980, SIEFERT et coll.).

CONCLUSIONS

Iohexol and ioxaglate seem to be well suited for aortofemoral

angiography as they cause significantly less pain, induce less hemodynamic effects and have a lower general toxicity than currently used ionic contrast media, provided that their price will be tolerable. They are both supplied as solutions and are as easy to handle as ionic monomers.

ACKNOWLEDGEMENTS

Sincere thanks are extended to Miss Agneta Edeborg, Miss Siv Granelli, Mrs. Anette Holmén and Miss Ulla-Lena Ringquist for technical assistance and to Mrs. Marie-Louise Tengryd at the department of vascular surgery for kind cooperation.

This project was partly supported by the Swedish Medical Research Council (Project No. 3483).

SUMMARY

Two new contrast media, iohexol (non-ionic monomer) and ioxaglate (monoacidic dimer), were compared with the non-ionic metrizamide during aortofemoral angiography in a single blind randomized trial in two groups of patients with 20 in each. The degree of heat and pain produced by iohexol and ioxaglate did not differ significantly from that produced by metrizamide, while subsequent injections of metrizoate caused significantly more heat and pain. The hemodynamic effects recorded in 10 patients in each group showed that iohexol and ioxaglate induced a decrease in vascular resistance, decrease in blood pressure and increase in heart rate not differing significantly from that induced by metrizamide.

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